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Search Results -

Terms	Documents
(vcam$ or vla adj 4 or vla4) same (herpes or arbovirus$ or borna)	3

Database: US Patents Full-Text Database; JPO Abstracts Database; EPO Abstracts Database; Derwent World Patents Index; IBM Technical Disclosure Bulletins

Refine Search: (vcam$ or vla adj 4 or vla4) same (herpes or arbovirus$ or borna) Clear

Search History

Today's Date: 7/23/2000

DB Name	Query	Hit Count	Set Name
USPT	(vcam$ or vla adj 4 or vla4) same (herpes or arbovirus$ or borna)	3	L2
USPT	(alpha adj 4 or alpha4 or vla adj 4 or vla4) same (herpes or arbovirus$ or borna)	18	L1

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Search Results - Record(s) 1 through 10 of 18 returned.

☐ 1. Document ID: US 6090626 A

L1: Entry 1 of 18 File: USPT Jul 18, 2000

US-PAT-NO: 6090626
DOCUMENT-IDENTIFIER: US 6090626 A

TITLE: Antisense oligonucleotide modulation of raf gene expression

DATE-ISSUED: July 18, 2000

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Monia; Brett P.	La Costa	CA	N/A	N/A
Boggs; Russell T.	Cardiff-by-the-Sea	CA	N/A	N/A

US-CL-CURRENT: 435/375; 514/44, 536/24.5

Full | Title | Citation | Front | Review | Classification | Date | Reference | Claims | KWIC | Draw Desc | Image

☐ 2. Document ID: US 6045803 A

L1: Entry 2 of 18 File: USPT Apr 4, 2000

US-PAT-NO: 6045803
DOCUMENT-IDENTIFIER: US 6045803 A

TITLE: Live recombinant avian vaccine using an avian herpesvirus as vector

DATE-ISSUED: April 4, 2000

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Audonnet; Jean-Christophe Francis	Lyons	N/A	N/A	FRX
Bublot; Michel Joseph Marie	St-Genis-les-Ollieres	N/A	N/A	FRX
Darteil; Raphael Jean	Lyons	N/A	N/A	FRX
Duinat; Carole Veronique	Lyons	N/A	N/A	FRX
Laplace; Eliane Louise	Oullins	N/A	N/A	FRX
Riviere; Michel Albert Emile	Fran.cedilla.oise	Ecully	N/A	N/A FR

US-CL-CURRENT: 424/199.1

Full | Title | Citation | Front | Review | Classification | Date | Reference | Claims | KWIC | Draw. Desc | Image

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☐ 3. Document ID: US 5998385 A

L1: Entry 3 of 18 File: USPT Dec 7, 1999

US-PAT-NO: 5998385
DOCUMENT-IDENTIFIER: US 5998385 A

TITLE: Antisense oligonucleotide modulation of raf gene expression

DATE-ISSUED: December 7, 1999(G)

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Monia; Brett P.	Carlsbad	CA	N/A	N/A
Martin; Pierre	Rheinfelden	N/A	N/A	CHX
Altmann; Karl-Heinz	Reinach	N/A	N/A	CHX

Full | Title | Citation | Front | Review | Classification | Date | Reference | Claims | KWIC | Draw. Desc | Image

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☐ 4. Document ID: US 5980906 A

L1: Entry 4 of 18 File: USPT Nov 9, 1999

US-PAT-NO: 5980906
DOCUMENT-IDENTIFIER: US 5980906 A

TITLE: Live recombinant avian vaccine using an avian herpesvirus as vector

DATE-ISSUED: November 9, 1999

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Audonnet; Jean-Christophe Francis	Lyons	N/A	N/A	FRX
Bublot; Michel Joseph Marie	St-Genis-les-Ollieres	N/A	N/A	FRX
Darteil; Raphael Jean	Lyons	N/A	N/A	FRX
Duinat; Carole Veronique	Lyons	N/A	N/A	FRX
Laplace; Eliane Louise	Oullins	N/A	N/A	FRX
Riviere; Michel Albert Emile	Fran.cedilla.oise Ecully	N/A	N/A	FR:

US-CL-CURRENT: 424/199.1; 424/204.1, 424/229.1, 435/235.1, 435/320.1, 435/69.1, 435/69.3, 435/71.1

Full | Title | Citation | Front | Review | Classification | Date | Reference | Claims | KWIC | Draw Desc | Image

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☐ 5. Document ID: US 5952229 A

L1: Entry 5 of 18 File: USPT Sep 14, 1999

US-PAT-NO: 5952229
DOCUMENT-IDENTIFIER: US 5952229 A

TITLE: Antisense oligonucleotide modulation of raf gene expression

DATE-ISSUED: September 14, 1999

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Monia; Brett P.	Carlsbad	CA	N/A	N/A
Boggs; Russell T.	Cardiff-By-The-Sea	CA	N/A	N/A

US-CL-CURRENT: 435/375; 514/44, 536/24.5

Full | Title | Citation | Front | Review | Classification | Date | Reference | Claims | KWIC | Draw Desc | Image

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☐ 6. Document ID: US 5876923 A

L1: Entry 6 of 18 File: USPT Mar 2, 1999

US-PAT-NO: 5876923
DOCUMENT-IDENTIFIER: US 5876923 A

TITLE: Herpes simplex virus ICP4 as an inhibitor of apoptosis

DATE-ISSUED: March 2, 1999

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Leopardi; Rosario	Chicago	IL	N/A	N/A
Roizman; Bernard	Chicago	IL	N/A	N/A

US-CL-CURRENT: 435/5; 424/93.1, 424/93.2, 435/6, 435/69.2, 514/44

Full | Title | Citation | Front | Review | Classification | Date | Reference | Claims | KWIC | Draw Desc | Image

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☐ 7. Document ID: US 5874279 A

L1: Entry 7 of 18 File: USPT Feb 23, 1999

US-PAT-NO: 5874279
DOCUMENT-IDENTIFIER: US 5874279 A

TITLE: Recombinant infectious bovine rhinotracheitis virus

DATE-ISSUED: February 23, 1999

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Cochran; Mark D.	Carlsbad	CA	N/A	N/A
Macdonald; Richard D.	San Diego	CA	N/A	N/A

US-CL-CURRENT: 435/235.1; 435/320.1

Full | Title | Citation | Front | Review | Classification | Date | Reference | Claims | KWIC | Draw Desc | Image

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☐ 8. Document ID: US 5853733 A

L1: Entry 8 of 18 File: USPT Dec 29, 1998

US-PAT-NO: 5853733
DOCUMENT-IDENTIFIER: US 5853733 A

TITLE: Recombinant herpesvirus of turkeys and uses thereof

DATE-ISSUED: December 29, 1998

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Cochran; Mark D.	Carlsbad	CA	N/A	N/A
Macdonald; Richard D.	San Diego	CA	N/A	N/A

US-CL-CURRENT: 424/199.1; 424/229.1, 424/816, 435/235.1, 435/320.1, 435/69.1, 435/69.3

Full | Title | Citation | Front | Review | Classification | Date | Reference | Claims | KWIC | Draw Desc | Image

☐ 9. Document ID: US 5846707 A

L1: Entry 9 of 18 File: USPT Dec 8, 1998

US-PAT-NO: 5846707
DOCUMENT-IDENTIFIER: US 5846707 A

TITLE: Herpes simplex virus as a vector

DATE-ISSUED: December 8, 1998

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Roizman; Bernard	Chicago	IL	N/A	N/A

US-CL-CURRENT: 435/5; 435/320.1, 435/465, 435/6, 435/69.1, 435/91.41

Full | Title | Citation | Front | Review | Classification | Date | Reference | Claims | KWIC | Draw Desc | Image

☐ 10. Document ID: US 5804372 A

L1: Entry 10 of 18 File: USPT Sep 8, 1998

US-PAT-NO: 5804372
DOCUMENT-IDENTIFIER: US 5804372 A

TITLE: Method of distinguishing an IBRV-vaccinated bovine from a bovine infected with a wild type virus

DATE-ISSUED: September 8, 1998

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Cochran; Mark D.	Carlsbad	CA	N/A	N/A
Macdonald; Richard D.	San Diego	CA	N/A	N/A

US-CL-CURRENT: 435/5; 424/229.1, 435/7.1

Full | Title | Citation | Front | Review | Classification | Date | Reference | Claims | KWIC | Draw Desc | Image

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Terms	Documents
(alpha adj 4 or alpha4 or vla adj 4 or vla4) same (herpes or arbovirus$ or borna)	18

Display 10 Documents, starting with Document: 11

Display Format: CIT Change Format

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Search Results - Record(s) 11 through 18 of 18 returned.

☐ 11. Document ID: US 5783195 A

L1: Entry 11 of 18 File: USPT Jul 21, 1998

US-PAT-NO: 5783195
DOCUMENT-IDENTIFIER: US 5783195 A

TITLE: Recombinant infectious bovine rhinotracheitis virus S-IBR-052 and uses thereof

DATE-ISSUED: July 21, 1998

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Cochran; Mark D.	Carlsbad	CA	N/A	N/A
Macdonald; Richard D.	San Diego	CA	N/A	N/A

US-CL-CURRENT: 424/229.1; 435/235.1, 435/236

Full | Title | Citation | Front | Review | Classification | Date | Reference | Claims | KWIC | Draw Desc | Image

☐ 12. Document ID: US 5744362 A

L1: Entry 12 of 18 File: USPT Apr 28, 1998

US-PAT-NO: 5744362
DOCUMENT-IDENTIFIER: US 5744362 A

TITLE: Antisense oligonucleotide modulation of raf gene expression

DATE-ISSUED: April 28, 1998

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Monia; Brett P.	Carlsbad	CA	N/A	N/A
Martin; Pierre	Rheinfelden	N/A	N/A	CHX
Altmann; Karl-Heinz	Reinach	N/A	N/A	CHX

US-CL-CURRENT: 435/375; 514/44, 536/24.5

Full | Title | Citation | Front | Review | Classification | Date | Reference | Claims | KWIC | Draw Desc | Image

☐ 13. Document ID: US 5733554 A

L1: Entry 13 of 18 File: USPT Mar 31, 1998

US-PAT-NO: 5733554
DOCUMENT-IDENTIFIER: US 5733554 A

TITLE: Avian herpesvirus-based live recombinant avian vaccine, in particular against Gumboro disease

DATE-ISSUED: March 31, 1998

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Audonnet; Jean-Christophe	Lyons	N/A	N/A	FRX
Bublot; Michel Joseph Marie	Lyons	N/A	N/A	FRX
Darteil; Raphael Jean	Lyons	N/A	N/A	FRX
Duinat; Carole Veronique	Oullins	N/A	N/A	FRX
Laplace; Eliane Louise	Ecully	N/A	N/A	FRX
Riviere; Michel Albert Emile				

Fran.cedilla.is Saint-Genis-Les-Ollieres N/A N/

Fran.cedilla.oise

US-CL-CURRENT: 424/199.1; 424/204.1, 424/229.1, 435/235.1, 435/320.1

Full | Title | Citation | Front | Review | Classification | Date | Reference | Claims | KWIC | Draw Desc | Image

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☐ 14. Document ID: US 5599676 A

L1: Entry 14 of 18 File: USPT Feb 4, 1997

US-PAT-NO: 5599676
DOCUMENT-IDENTIFIER: US 5599676 A

TITLE: Method for isolating a novel receptor for .alpha.4 integrins

DATE-ISSUED: February 4, 1997

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Vonderheide; Robert H.	Brookline	MA	N/A	N/A
Springer; Timothy A.	Chestnut Hill	MA	N/A	N/A

US-CL-CURRENT: 435/7.2; 435/252.3, 435/252.33, 435/254.11, 435/320.1, 435/69.1, 435/91.1, 530/387.1, 536/23.1

Full | Title | Citation | Front | Review | Classification | Date | Reference | Claims | KWIC | Draw Desc | Image

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☐ 15. Document ID: US 5599544 A

L1: Entry 15 of 18 File: USPT Feb 4, 1997

US-PAT-NO: 5599544
DOCUMENT-IDENTIFIER: US 5599544 A

TITLE: Recombinant infectious bovine rhinotracheitis virus

DATE-ISSUED: February 4, 1997

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Cochran; Mark D.	Carlsbad	CA	N/A	N/A
Macdonald; Richard D.	San Diego	CA	N/A	N/A

US-CL-CURRENT: 424/229.1; 435/235.1

Full | Title | Citation | Front | Review | Classification | Date | Reference | Claims | KWIC | Draw Desc | Image

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☐ 16. Document ID: US 5593873 A

L1: Entry 16 of 18 File: USPT Jan 14, 1997

US-PAT-NO: 5593873
DOCUMENT-IDENTIFIER: US 5593873 A

TITLE: Recombinant infectious bovine rhinotracheitis virus

DATE-ISSUED: January 14, 1997

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Cochran; Mark D.	Carlsbad	CA	N/A	N/A
Macdonald; Richard D.	San Diego	CA	N/A	N/A

US-CL-CURRENT: 435/235.1; 435/320.1

Full | Title | Citation | Front | Review | Classification | Date | Reference | Claims | KWIC | Draw Desc | Image

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☐ 17. Document ID: US 5495006 A

L1: Entry 17 of 18 File: USPT Feb 27, 1996

US-PAT-NO: 5495006
DOCUMENT-IDENTIFIER: US 5495006 A

TITLE: Antiviral polynucleotide conjugates

DATE-ISSUED: February 27, 1996

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Climie; Shane	Toronto	N/A	N/A	CAX
Ma; Michael	Etobicoke	N/A	N/A	CAX

US-CL-CURRENT: 536/24.1; 435/5, 536/23.1

Full | Title | Citation | Front | Review | Classification | Date | Reference | Claims | KWIC | Draw Desc | Image

☐ 18. Document ID: US 5324664 A

L1: Entry 18 of 18 File: USPT Jun 28, 1994

US-PAT-NO: 5324664
DOCUMENT-IDENTIFIER: US 5324664 A

TITLE: Herpes virus thymidien kinase-encoding DNA

DATE-ISSUED: June 28, 1994

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Nunberg; Jack H.	San Carlos	CA	N/A	N/A
Post; Leonard E.	Ann Arbor	MI	N/A	N/A
Compton; Teresa	Madison	WI	N/A	N/A
Petrovskis; Erik A.	Ann Arbor	MI	N/A	N/A

US-CL-CURRENT: 435/320.1; 435/235.1, 435/69.1, 530/350, 536/23.1, 536/23.72, 536/24.1

Full | Title | Citation | Front | Review | Classification | Date | Reference | Claims | KWIC | Draw Desc | Image

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Terms	Documents
(alpha adj 4 or alpha4 or vla adj 4 or vla4) same (herpes or arbovirus$ or borna)	18

Display 10 Documents, starting with Document: 18

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L2: Entry 1 of 3 File: USPT Sep 28, 1999

DOCUMENT-IDENTIFIER: US 5958406 A
TITLE: Acne treatment with multifunctional enzyme

BSPR:
The invention further provides (a) methods for treating or prophylactically preventing a cell-cell or cell-virus adhesion syndrome comprising administering an anti-adhesion effective amount of a hydrolase effective to remove or inactivate a cellular or viral acceptor or receptor adhesion component that is involved in the cell-cell or cell-virus adhesion, (b) compositions or substances for use in such methods, (c) pharmaceutical compositions containing effective amounts of enzyme for use in such methods, and (d) uses of the enzyme composition for manufacturing a medicament for use in such methods. Preferably, the syndrome comprises inflammation, shock, tumor metastases, autoimmune disease, transplantation rejection reactions or microbial infections. Preferably, (a) the syndrome is selected from the group consisting of microbial infection, immune disorder, cystic fibrosis, COPD, atherosclerosis, cancer, asthma, septic shock, toxic shock syndrome, conjunctivitis, reperfusion injury and pain, and (b) a cell surface receptor, associated with the cell-cell or cell-virus adhesion syndrome, selected from the group consisting of ICAM-1, ICAM-2, VCAM-1, CD4, CD8, CD11, CD18, CD28, CD29D, CD31, CD44, CD 49, CD62L, CD102 and asialo GM1 ceramide is removed or inactivated by the administered hydrolase. Preferably, a microbial infection is treated or prevented and the microbial infection is a herpes, HIV, hepatitis or papilloma infection; an infection causing colitis, ulcer or diarrhoea; a candida infection, such as an oral, vaginal or esophageal candida infection; a cold or influenza infection; a pseudomonas, haemophilus, staphylococcus, streptococcus, klebsiella or E. coli infection; a primary or secondary infection of leprosy; or an infection causing conjunctivitis.

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L2: Entry 1 of 3 File: USPT Sep 28, 1999

US-PAT-NO: 5958406
DOCUMENT-IDENTIFIER: US 5958406 A
TITLE: Acne treatment with multifunctional enzyme
DATE-ISSUED: September 28, 1999

US-CL-CURRENT: 424/94.63; 424/94.6, 435/226, 435/264

APPL-NO: 8/ 600273
DATE FILED: February 8, 1996

PARENT-CASE:
This application is a continuation-in-part of U.S. application Ser. No. 08/486,820, filed Jun. 7, 1995, which is a continuation-in-part of U.S. application Ser. No. 08/385,540, filed Feb. 8, 1995, titled "Crustacean and Fish Derived Multifunctional Enzyme" which is a continuation-in-part of Ser. No. 08/388,501 filed Nov. 22, 1994, now abandoned.

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L2 23 DUP REM L1 (28 DUPLICATES REMOVED)

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L2 ANSWER 1 OF 23 CAPLUS COPYRIGHT 2000 ACS
ACCESSION NUMBER: 2000:141480 CAPLUS
DOCUMENT NUMBER: 132:189685
TITLE: Krill-derived multifunctional enzyme and its medical uses
INVENTOR(S): De Faire, Johan R.; Franklin, Richard L.; Kay, John; Lindblom, Ragnvald
PATENT ASSIGNEE(S): Phairson Medical Inc., UK
SOURCE: U.S., 41 pp., Cont.-in-part of U.S. Ser. No. 385,450.

CODEN: USXXAM
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 4
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 6030612	A	20000229	US 1995-486820	19950607
US 5945102	A	19990831	US 1995-385540	19950208
CA 2212533	AA	19960815	CA 1996-2212533	19960208
WO 9624371	A1	19960815	WO 1996-US1650	19960208
W: AL, AM, AU, BB, BG, BR, CA, CN, CZ, EE, FI, GE, HU, IS, JP, KG, KP, KR, LK, LR, LT, LV, MD, MG, MK, MN, MX, NO, NZ, PL, RO, SG, SI, SK, TR, TT, UA, UZ, VN, AZ, BY, KG, KZ, RU, TJ, TM				
RW: KE, LS, MW, SD, SZ, UG, AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG				
AU 9649170	A1	19960827	AU 1996-49170	19960208
AU 718220	B2	20000413		
EP 810875	A1	19971210	EP 1996-905398	19960208
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV				
BR 9607506	A	19971223	BR 1996-7506	19960208
CN 1181018	A	19980506	CN 1996-193103	19960208
JP 11502102	T2	19990223	JP 1996-524401	19960208
US 5958406	A	19990928	US 1996-600273	19960208
NO 9703627	A	19971007	NO 1997-3627	19970806
PRIORITY APPLN. INFO.:			US 1994-338501	19941122
			US 1995-385540	19950208
			US 1995-486820	19950607
			WO 1996-US1650	19960208

AB The invention relates to a multifunctional enzyme that can be derived from crustaceans or fish. The enzyme has at least one of a chymotrypsin, trypsin, elastase, collagenase and exo peptidase activity, and a mol. wt. between about 20 kDa and about 40 kDa as detd. by SDS-PAGE. Preferably, the multifunctional enzyme has substantial anti cell-cell adhesion activity. Preferably, the multifunctional enzyme has substantial homol. with the krill multifunctional enzyme. These enzymes are useful for treating viral infections such as **herpes** outbreaks, fungal, bacterial or parasitic infections, including the primary and secondary infections of leprosy, colitis, ulcers, hemorrhoids, corneal scarring, dental plaque, acne, cystic fibrosis, blood clots, wounds, immune disorders including autoimmune disease and cancer. Addnl., the invention relates to a method of purifying the multifunctional enzyme, and to a prepn. of essentially purified multifunctional enzyme.

REFERENCE COUNT: 80
REFERENCE(S):
(2) Anheller; Archives of Dermatology Research 1989, V281, P105 CAPLUS
(3) Anon; EP 170115 A1 1985 CAPLUS
(5) Anon; WO 9319732 1993 CAPLUS
(6) Anon; WO 9324142 1993 CAPLUS
(8) Anon; WO 9507686 1995 CAPLUS
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L2 ANSWER 2 OF 23 MEDLINE DUPLICATE 1
ACCESSION NUMBER: 2000253149 MEDLINE
DOCUMENT NUMBER: 20253149
TITLE: Interferon-gamma up-regulates intercellular adhesion molecule-1 and vascular cell adhesion molecule-1 and recruits lymphocytes into the vagina of immune mice challenged with **herpes** simplex virus-2.
AUTHOR: Parr M B; Parr E L
CORPORATE SOURCE: Department of Anatomy, School of Medicine, Southern Illinois University, Carbondale, IL 62901, USA.

CONTRACT NUMBER: HD 17337 (NICHD)
SOURCE: IMMUNOLOGY, (2000 Apr) 99 (4) 540-5.
Journal code: GH7. ISSN: 0019-2805.
PUB. COUNTRY: ENGLAND: United Kingdom
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals; Cancer Journals
ENTRY MONTH: 200008
ENTRY WEEK: 20000801

AB Lymphocyte recruitment into tissues involves interactions between adhesion molecules on vascular endothelial cells and corresponding ligands on the lymphocyte surface. In the present study we investigated the expression of four endothelial addressins in the vagina and their possible up-regulation by interferon-gamma (IFN-gamma) in immune mice after vaginal challenge with **herpes** simplex virus type 2. The adhesion molecules intercellular adhesion molecule-1 (ICAM-1) and vascular cell adhesion molecule-1 (**VCAM**-1) were minimally expressed in the vagina of non-immune mice with or without vaginal challenge and in immune mice before challenge, but both were up-regulated by IFN-gamma, directly or indirectly, in immune mice after challenge. Mucosal addressin cell adhesion molecule-1 (MAdCAM-1) was detected in most vaginas but was not up-regulated by IFN-gamma in immune mice after virus challenge. E-selectin was not detected in any vaginas. The results suggest that ICAM-1 and **VCAM**-1 may be involved in rapid, IFN-gamma-mediated recruitment of lymphocytes to the vaginal mucosal of immune mice after local virus challenge.

L2 ANSWER 3 OF 23 CAPLUS COPYRIGHT 2000 ACS
ACCESSION NUMBER: 1999:622175 CAPLUS
DOCUMENT NUMBER: 131:237988
TITLE: Acne treatment with krill-derived multifunctional enzyme
INVENTOR(S): De Faire, Johan R.; Franklin, Richard L.; Kay, John; Lindblom, Ragnvald
PATENT ASSIGNEE(S): Phairson Medical Inc., UK
SOURCE: U.S., 42 pp., Cont.-in-part of U.S. Ser. No. 486,820.
CODEN: USXXAM
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 4
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 5958406	A	19990928	US 1996-600273	19960208
US 5945102	A	19990831	US 1995-385540	19950208
US 6030612	A	20000229	US 1995-486820	19950607
PRIORITY APPLN. INFO.:			US 1994-338501	19941122
			US 1995-385540	19950208
			US 1995-486820	19950607

AB The invention relates to a multifunctional enzyme that can be derived from crustaceans or fish. The enzyme has at least one of a chymotrypsin, trypsin, elastase, collagenase and exo peptidase activity, and a mol. wt. between about 20 kd and about 40 kd as detd. by SDS PAGE. Preferably, the multifunctional enzyme has substantial anti cell-cell adhesion activity. Preferably, the multifunctional enzyme has substantial homol. with the krill multifunctional enzyme. These enzymes are useful for treating viral infections such as **herpes** outbreaks, fungal, bacterial or parasitic infections, including the primary and secondary infections of

leprosy, colitis, ulcers, hemorrhoids, corneal scarring, dental plaque, acne, cystic fibrosis, blood clots, wounds, immune disorders including autoimmune disease and cancer. Addnl., the invention relates to a method of purifying the multifunctional enzyme, and to a prepn. of essentially purified multifunctional enzyme. Women with facial acne were treated with 0.1 mg of krill multifunctional hydrolase prepn. several times a day for 4-6 days.

REFERENCE COUNT: 79

REFERENCE(S):
(2) Anheller; Arch Dermatol Res 1989, V281, P105 CAPLUS
(3) Anheller; Archives of Dermatology Research 1989, V281, P105 CAPLUS
(4) Anon; EP 0170115 A1 1985 CAPLUS
(6) Anon; WO 9319732 1993 CAPLUS
(7) Anon; WO 9324142 1993 CAPLUS

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L2 ANSWER 4 OF 23 CAPLUS COPYRIGHT 2000 ACS

ACCESSION NUMBER: 1998:268677 CAPLUS
DOCUMENT NUMBER: 128:319071
TITLE: Growth of B cell lymphomas on HIV-infected endothelial cells
INVENTOR(S): Nelson, Jay; Moses, Ashlee; Bagby, Grover
PATENT ASSIGNEE(S): Oregon Health Sciences University, USA; Nelson, Jay; Moses, Ashlee; Bagby, Grover
SOURCE: PCT Int. Appl., 42 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9818004	A1	19980430	WO 1997-US19323	19971023
W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG				
AU 9749190	A1	19980515	AU 1997-49190	19971023
PRIORITY APPLN. INFO.:			US 1996-29605	19961024
			WO 1997-US19323	19971023

AB The present invention provides methods of stimulating proliferation of neoplastic B cells, methods of screening for inhibitors of neoplastic B cells, and co-cultures of neoplastic B cells and endothelial cells transduced with a viral nucleic acid. Neoplastic B cell are derived from bone marrow, ascites fluid, lymphoid tissue, or peripheral mononuclear blood cells. Microvascular endothelial cells are obtained from bone marrow aspirates, brain tissue, skin tissue, lung tissue, or macrovascular endothelial cells are obtained from aorta tissue or umbilical cord tissue.

The virus nucleic acid is HIV, human **herpes** virus 8, cytomegalovirus, or Epstein-Barr virus. The inhibitors for screening are compds. that inhibit CD40, CD40L, **VCAM**-1, **VLA**-4, LFA-1, ICAM-1, CD44, hyaluran, and Tat, Nef, Rev, Vpr, Vpu or gp120 viral proteins.

L2 ANSWER 5 OF 23 MEDLINE DUPLICATE 2

ACCESSION NUMBER: 1998290422 MEDLINE

DOCUMENT NUMBER: 98290422
TITLE: In vivo treatment with anti-alpha4 integrin suppresses clinical and pathological evidence of **Borna** disease virus infection.
AUTHOR: Rubin S A; Yednock T A; Carbone K M
CORPORATE SOURCE: Department of Medicine, The Johns Hopkins University School of Medicine, Baltimore, MD, USA.
CONTRACT NUMBER: NS289599 (NINDS)
MH48948 (NIMH)
SOURCE: JOURNAL OF NEUROIMMUNOLOGY, (1998 Apr 15) 84 (2) 158-63. Journal code: HSO. ISSN: 0165-5728.
PUB. COUNTRY: Netherlands
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199808
ENTRY WEEK: 19980804
AB **Borna** disease virus (BDV) infection of the rat brain induces a severe T-lymphocyte mediated inflammatory response that parallels the course of clinical **Borna** disease. In other models of CNS inflammation, the recruitment of T-lymphocytes from the circulation to sites of inflammation is believed to be directed, in part, by the cellular adhesion molecules alpha4 beta1 integrin (expressed on T-lymphocytes) and its ligand **VCAM**-1 (expressed on blood brain barrier endothelium). Since BDV-specific T-lymphocytes are known to express the alpha4 beta1 integrin, we examined the effect of in vivo treatment with an anti-alpha4 integrin monoclonal antibody (GG5/3) on the development of BDV-specific encephalitis and **Borna** disease. Here, we report that the inhibition of alpha4 integrin provided significant clinical benefit in slowing the progression of **Borna** disease. Antibody treatment greatly reduced the immune cell infiltrates in the CNS of BDV-infected animals, but we found that this inhibition of the immune response did not result in enhanced viral levels.

L2 ANSWER 6 OF 23 MEDLINE DUPLICATE 3
ACCESSION NUMBER: 1998180905 MEDLINE
DOCUMENT NUMBER: 98180905
TITLE: Evidence for deficiencies in intracerebral cytokine production, adhesion molecule induction, and T cell recruitment in **herpes** simplex virus type-2 infected mice.
AUTHOR: Lewandowski G; Hobbs M V
CORPORATE SOURCE: Department of Neuropharmacology, The Scripps Research Institute, La Jolla, CA 92037, USA.
CONTRACT NUMBER: R29MH51926 (NIMH)
AG09822 (NIA)
SOURCE: JOURNAL OF NEUROIMMUNOLOGY, (1998 Jan) 81 (1-2) 58-65. Journal code: HSO. ISSN: 0165-5728.
PUB. COUNTRY: Netherlands
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199806
ENTRY WEEK: 19980603
AB We examined the intracerebral T cell response in mice infected with neurovirulent HSV-2 strains and an avirulent HSV-1. In HSV-2-infected brains, (i) IL-1beta, TNF-alpha and IFN-gamma mRNA expression was low, (ii) ICAM-1 and **VCAM**-1 were not induced, (iii) few CD4+ or CD8+ cells were detected. By contrast, in HSV-1-infected brains, (i) cytokine mRNA expression was high, (ii) adhesion molecules were strongly expressed, (iii) many T cells were detected. We suggest that deficient T cell extravasation into HSV-2-infected brain regions is caused by negligible

ICAM-1 and **VCAM**-1 expression, which is due to low expression of critical cytokines.

L2 ANSWER 7 OF 23 MEDLINE DUPLICATE 4
ACCESSION NUMBER: 1998071120 MEDLINE
DOCUMENT NUMBER: 98071120
TITLE: Influence of viral infection on expression of cell surface antigens in human retinal pigment epithelial cells.
AUTHOR: Larcher C; Recheis H; Sgonc R; Gottinger W; Huemer H P; Irschick E U
CORPORATE SOURCE: Institute of Hygiene, University of Innsbruck, Austria.
SOURCE: GRAEFES ARCHIVE FOR CLINICAL AND EXPERIMENTAL OPHTHALMOLOGY, (1997 Nov) 235 (11) 709-16.
Journal code: FPR. ISSN: 0721-832X.
PUB. COUNTRY: GERMANY: Germany, Federal Republic of
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199803
ENTRY WEEK: 19980305
AB BACKGROUND: Subacute viral infection is known to change the phenotype of infected cells, thereby causing immune-mediated tissue damage. The aim of this study was to investigate the expression of different cell surface molecules on human retinal pigment epithelial cells (RPEC) following viral infection, with special emphasis on those having immune-regulatory functions. METHODS: Cultured RPEC were infected with cytomegalovirus (CMV), coxsackie-virus B3 (CVB) or **herpes** simplex virus type I (HSV). Double-staining fluorescence technique was used for visualization of virus infection and cell surface markers in the same cells by laser microscopy. RESULTS: CMV downregulated MHC class I antigens on RPEC, whereas CVB and HSV did not alter MHC class I antigen expression. No induction of class II antigens was observed in RPEC infected with CVB, HSV or CMV. The intercellular adhesion molecule ICAM-1 (CD54) was strongly expressed in uninfected RPEC, and a slight increase was observed after virus infection. Vascular cell adhesion molecule 1 (**VCAM**-1) was expressed in low amounts in both uninfected and infected RPEC. No expression of intercellular adhesion molecule 2 (ICAM-2), E-selectin ELAM-1 or lymphocyte-function-associated antigen 1 (LFA-1) was observed on RPEC before or after virus infection. CONCLUSION: Downmodulation of immune-regulating cell surface antigens has been suggested to provide a means of long-term survival of viruses in the infected cell, favoring establishment of persistent infection. Our observation in cultured human RPEC indicates that this mechanism might indeed contribute to the development of disease affecting retinal tissue.

L2 ANSWER 8 OF 23 MEDLINE DUPLICATE 5
ACCESSION NUMBER: 1998173992 MEDLINE
DOCUMENT NUMBER: 98173992
TITLE: Immunohistochemical examination of intracerebral T cell recruitment and adhesion molecule induction in **herpes** simplex virus-infected mice.
AUTHOR: Lewandowski G
CORPORATE SOURCE: Department of Neuropharmacology, Scripps Research Institute, La Jolla, California 92037, USA.. glewandowski@scripps.edu
CONTRACT NUMBER: R29MH51926 (NIMH)
SOURCE: BRAIN, BEHAVIOR, AND IMMUNITY, (1997 Dec) 11 (4) 264-72.
Journal code: BBI. ISSN: 0889-1591.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199807

ENTRY WEEK: 19980703
AB **Herpes** simplex virus type 1 (HSV-1) infection in the nervous system is tightly controlled by the T-cell-mediated response. This report describes the temporal relationships among HSV-1 infection, intracerebral adhesion molecule induction, and T cell migration in intravitreally inoculated mice. HSV-1 immunoreactivity, initially detected at 3 days, increased in area and intensity in the superior colliculus, oculomotor nucleus, and geniculate through 5 days. By 6 days, HSV-1 was nearly undetectable in the same regions and the mice survive the infection. At the peak of HSV-1 immunoreactivity, ICAM-1 and **VCAM**-1 were strongly expressed in all infected brain regions. Additionally, in these region a few CD4+ and CD8+ T cells were detected. The heaviest T cell migration and adhesion molecule expression occurred at 6 days, coinciding with the decrease in HSV-1 immunoreactivity. However, in SCID and athymic mice, HSV-1 was not cleared from the brain and the mice died. Together, these data suggest that HSV-1 infection of the brain is followed by adhesion molecule induction in and T cell extravasation into the infected brain regions. Most importantly, an efficient T cell response was required to eradicate infectious HSV-1 from the brain.

L2 ANSWER 9 OF 23 BIOSIS COPYRIGHT 2000 BIOSIS
ACCESSION NUMBER: 1997:88010 BIOSIS
DOCUMENT NUMBER: PREV199799379723
TITLE: Therapy with antibody against leukocyte integrin **VLA**-4 (CD49d) is effective and safe in virus-facilitated experimental allergic encephalomyelitis.
AUTHOR(S): Soilu-Hanninen, M. (1); Roytta, M.; Salmi, A.; Salonen, R.
CORPORATE SOURCE: (1) Dep. Virology, Univ. Turku, Kiinamyllynkatu 13, FIN-20520 Turku Finland
SOURCE: Journal of Neuroimmunology, (1997) Vol. 72, No. 1, pp. 95-105.
ISSN: 0165-5728.
DOCUMENT TYPE: Article
LANGUAGE: English
AB Experimental allergic encephalomyelitis (EAE) is facilitated in resistant BALB/c mice by intraperitoneal infection with an avirulent Semliki Forest virus (SFV-A7). Viral infection increases the incidence of EAE from 15-30% to 60-90% and speeds up appearance of paralysis from 24 to 14 days. In this paper, we describe treatment of virus-facilitated EAE with monoclonal antibodies (mAbs) against leukocyte and/or endothelial cell adhesion molecules. Therapy with mAb against ICAM-1 (intercellular adhesion molecule-1) had a modest effect, but caused hemorrhagic brain and spinal cord lesions. Therapy with mAb against Mac-1 (alpha-M beta-2-integrin) was well tolerated but had no effect. Therapy with mAb against **VLA**-4 (alpha-4-beta-1-integrin) was safe, diminished both clinical and histopathological signs of EAE, decreased induction of **VCAM**-1 (vascular cell adhesion molecule-1) on brain vessels and diminished infiltration of **VLA**-4+ cells into the brain. The amount of viral antigen in the brain was riot altered. We conclude that facilitation of leukocyte entry into the brain is a major mechanism for viral facilitation of EAE in the BALB/c mouse, and that facilitation can be inhibited by anti-adhesion therapy. This may have implications for treatment of relapses triggered by viral infections in multiple sclerosis.

L2 ANSWER 10 OF 23 AIDSLINE
ACCESSION NUMBER: 1997:3253 AIDSLINE
DOCUMENT NUMBER: ICA11-96923610
TITLE: The relationship of dietary micronutrient intake to disease progression in a cohort of HIV+ gay men.

AUTHOR: Denotter D M; Strathdee S A; Craib K J; Cornelisse P G; Hogg R S; Rabound J M; O'Shaughnessy M V; Schechter M T
CORPORATE SOURCE: BC Centre for Excellence in HIV/AIDS, St. Paul's Hospital, Vancouver, BC, Canada.
SOURCE: Int Conf AIDS, (1996). Vol. 11, No. 2, pp. 101 (Abstract No. We.B.3259).
PUB. COUNTRY: Canada
DOCUMENT TYPE: (MEETING ABSTRACTS)
FILE SEGMENT: ICA11
LANGUAGE: English
ENTRY MONTH: 199701

AB Objective: To examine the potential relationship between dietary vitamin and mineral intake, particularly vitamin A, and progression of HIV infection within the Vancouver Lymphadenopathy-AIDS Study (**VLAS**). Methods: The dietary intake of 158 seropositive (SP) men was evaluated utilizing a self-administered 24-hour dietary recall questionnaire at baseline between October 1991 and September 1992. Macro and micronutrient content of each food item was coded using a nutritional analysis computer software package based on the Canadian Nutrient File database. All micronutrients were compared to the 1990 Canadian Recommended Nutrient Intake (RNI). Subjects who were free of minor opportunistic infection (diarrhea, oral thrush, hairy leukoplakia, peripheral nueropathy and **herpes** zoster) at baseline, were followed to see whether vitamin A intake, in particular, was related to future incidence of one of these events. Time to a drop below 500 cells/mm3 for those men with CD4 counts above 500 at baseline, and a 33% decline in CD4 counts for those men whose CD4 level was below 500, was also examined based on vitamin A intake. The number of AIDS defining illnesses in the AIDS free population was examined for all micronutrients. Follow-up time ranged from 24 to 36 months. Results: The mean dietary micronutrient intake for SP subjects was significantly lower than the RNI for zinc and vitamin E. The number of events of minor opportunistic infection was not significantly different in those subjects with high vs. low intake of Vitamin A, using both the RNI and the 67th percentile as cutoff points. Changes in CD4 count over time were not significantly associated with vitamin A. However, Kaplan-Meier curves and log rank scores testing the effect of micronutrient intake on time to diagnosis of an AIDS defining illness showed calcium, zinc and vitamin E to be marginally significant. Conclusions: Our analysis shows negative results for the effect of Vitamin A intake on disease progression and clinical endpoints in SP men; however, interesting findings regarding the effects of other dietary vitamin and mineral intake, particularly vitamin E, zinc and calcium need further investigation.

L2 ANSWER 11 OF 23 AIDSLINE
ACCESSION NUMBER: 1996:11337 AIDSLINE
DOCUMENT NUMBER: AIDS-96920525
TITLE: Longterm nonprogression among a cohort of HIV-infected homosexual men.
AUTHOR: Strathdee S A; Craib K J; Hogg R S; O'Shaughnessy M V; Montaner J S; Schechter M T
CORPORATE SOURCE: BC Centre for Excellence in HIV/AIDS & UBC, Vancouver.
SOURCE: Conf Retroviruses Opportunistic Infect, (1996). Vol. 3rd.
PUB. COUNTRY: United States
DOCUMENT TYPE: (MEETING ABSTRACTS)
FILE SEGMENT: AIDS
LANGUAGE: English
ENTRY MONTH: 199611

AB Objective: To evaluate longterm nonprogression (LTNP) in a prospective cohort of 329 HIV-infected homosexual men in the Vancouver Lymphadenopathy AIDS Study (**VLAS**). Methods: Evidence of HIV effect was defined as one or more of the following: (1) an AIDS-defining illness (ADI); (2)

thrush, **herpes** zoster or oral hairy leukoplakia (OIs); (3) a CD4 count less than 500/uL together with antiretroviral therapy and/or prophylaxis against PCP; (4) CD4 counts less than 500 cells/uL replicated on at least the 2 most recent tests; or (5) a negative CD4 slope over time significantly different from zero (p less than 0.05). Results: Of 346 men who were or became HIV-infected since 1982, 3 died of non-AIDS related causes and health status could not be determined within the last 2 yrs for 14 men. Of 329 men with known status, 321 (97.5%) experienced at least 1 of the above HIV effects. The most advanced criteria met by these men were 182 ADIs, 68 OIs, 22 had CD4s less than 500 and received treatment, 23 had CD4s less than 500 on their two most recent tests, and 26 had a significant CD4 decline. Of the remaining 8 subjects, 3 had a single CD4 less than 500uL Only 3 of 329 (0.9%) were infected for greater than 10 yrs without experiencing any of the above criteria. Conclusions: LTNP appears to be a rare phenomenon and may represent the tail end of a more or less continuous distribution of rates of disease progression, rather than a distinct subgroup. Even if all 14 men with unknown status were free of the specified HIV effects, then the maximal estimate for this favorable response would be 5%.

L2 ANSWER 12 OF 23 CAPLUS COPYRIGHT 2000 ACS
ACCESSION NUMBER: 1996:649649 CAPLUS
DOCUMENT NUMBER: 125:293026
TITLE: Induction of E-selectin for targeting therapeutic agents to disease-associated vascular endothelial cells
INVENTOR(S): Hallahan, Dennis E.; Weichselbaum, Ralph R.
PATENT ASSIGNEE(S): Arch Development Corporation, USA
SOURCE: PCT Int. Appl., 140 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9625947	A2	19960829	WO 1996-US2796	19960221
WO 9625947	A3	19970123		
W: AL, AM, AT, AU, BB, BG, BR, BY, CA, CH, CN, CZ, DE, DK, EE, ES, FI, GB, GE, HU, IS, JP, KE, KG, KP, KR, KZ, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK				
RW: KE, LS, MW, SD, SZ, UG, AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG				
US 5962424	A	19991005	US 1995-392541	19950221
AU 9651782	A1	19960911	AU 1996-51782	19960221
PRIORITY APPLN. INFO.:			US 1995-392541	19950221
			WO 1996-US2796	19960221

AB The present invention provides methods and compns. for use in specifically targeting disease (e.g. tumor)-assocd. vasculature endothelial cells, thereby delivering selected therapeutic and diagnostic agents to the vasculature. The invention requires the induction of the mol. E-selectin in tumor vasculature endothelial cells, as may be achieved using ionizing radiation, which then allows the selecting to be targeted using specific binding compns. and selected agents. The invention therefore provides methods for delivering a selected agent to the vasculature of an animal or

human subject comprising inducing E-selecting expression in vascular endothelial cells and administering to the animal a compn. comprising an E-selectin targeting component operatively assocd. with or attached to a selected agent. The currently preferred methods involve E-selectin induction.

L2 ANSWER 13 OF 23 BIOSIS COPYRIGHT 2000 BIOSIS
ACCESSION NUMBER: 1996:350273 BIOSIS
DOCUMENT NUMBER: PREV199699072629
TITLE: Therapy with antibody against leukocyte integrin **VLA**-4 is effective and safe in virus facilitated EAE.
AUTHOR(S): Soilu-Hanninen, Merja; Roytta, Matias; Salmi, Aimo; Salonen, Reijo
CORPORATE SOURCE: Dep. Virol., Univ. Turku, Kiinamyllynkatu 13, 20520 Turku Finland
SOURCE: Scandinavian Journal of Immunology, (1996) Vol. 43, No. 6, pp. 727.
Meeting Info.: XXVIIth Meeting of the Scandinavian Society for Immunology Turku, Finland May 24-27, 1996
ISSN: 0300-9475.
DOCUMENT TYPE: Conference
LANGUAGE: English

L2 ANSWER 14 OF 23 CANCERLIT
ACCESSION NUMBER: 97600818 CANCERLIT
DOCUMENT NUMBER: 97600818
TITLE: Apoptosis mediated cytokine release occurs in mediated bystander effect (Meeting abstract).
AUTHOR: Abboud C N; Rosell K F; Liesveld J L; Freeman S M
CORPORATE SOURCE: University of Rochester School of Medicine, Rochester, NY 14642.
SOURCE: Proc Annu Meet Am Soc Clin Oncol, (1996). Vol. 15, pp. A582.
ISSN: 0732-183X.
DOCUMENT TYPE: (MEETING ABSTRACTS)
FILE SEGMENT: ICDB
LANGUAGE: English
ENTRY MONTH: 199702
AB The application of suicide gene therapy to refractory malignancies relies on the demonstrated bystander effect in vivo and in vitro. In this model, cancer cells that express the **herpes** simplex thymidine kinase (HSV-TK) suicide gene kill nearby untransduced tumor cells after exposure to ganciclovir (Cancer Res; 53:5274 1993). While direct gap junctions may be involved in that process, a local inflammatory cellular response is also recruited at the site. The ovarian cancer cell line PA1, the fibrous histiocytoma line GCT, and colon carcinoma line HCT, expressing the HSV-TK gene, undergo programmed cell death after treatment with 50 uM ganciclovir. Apoptosis was quantified by flow cytometry and in situ terminal deoxynucleotidyl transferase assays. Cell death was associated with increased release of cytokines and chemokines from these tumor cells.
In particular, GCT-STK cells released interleukin-1 alpha and beta, interleukin-6, interleukin-8 (IL-8) and the chemokine Rantes. Similarly, the ovarian cancer PA1-STK cell line, released IL-1alpha, IL-1beta and IL-8. These cytokines may mediate the hemorrhagic tumor necrosis that is seen in vivo, in models of the bystander effect. This hypothesis was underscored by the upregulation of cellular adhesion receptors (ICAM-1, **VCAM**-1 and ELAM-1) on human umbilical vein endothelial cells (HUVECS) exposed to conditioned media from HSV-TK transduced cells undergoing apoptosis. Moreover, in the case of the colon adenocarcinoma HCT-STK cell line, tissue factor was also upregulated on the surface of HUVECS six hours after addition of ganciclovir treated supernatant. Taken together these findings provide an explanation for the multiple inflammatory pathways triggered in vivo by the application of suicide gene

therapy, manifested by the bystander effect. They also underscore the potential benefits (interference with tumor vascular integrity) and risks (local inflammation/hemorrhage) of such therapy when applied to solid tumors. (C) American Society of Clinical Oncology 1997

L2 ANSWER 15 OF 23 BIOSIS COPYRIGHT 2000 BIOSIS
ACCESSION NUMBER: 1996:157586 BIOSIS
DOCUMENT NUMBER: PREV199698729721
TITLE: Cytokines, adhesion molecules, and cellular infiltration in nephropathia epidemica kidneys: An immunohistochemical study.
AUTHOR(S): Temonen, Mari; Mustonen, Jukka; Helin, Heikki; Pasternack, Amos; Vaheri, Antti; Holthofer, Harry
CORPORATE SOURCE: Dep. Virology, Haartman Inst., POB 21, FIN-00014 Helsinki Univ., Helsinki Finland
SOURCE: Clinical Immunology and Immunopathology, (1996) Vol. 78, No. 1, pp. 47-55.
ISSN: 0090-1229.
DOCUMENT TYPE: Article
LANGUAGE: English
AB Puumala hantavirus-induced nephropathia epidemica (NE) is an important cause for an acute reversible renal failure in Scandinavia, European Russia, and the Balkans. The characteristic histopathological renal finding is an acute tubulointerstitial nephritis. Mild to massive proteinuria, hematuria, and a rise in the serum creatinine level are typically seen. The pathogenetic mechanisms of NE kidney failure are incompletely understood. Therefore we studied the infiltrating cell populations and local expression of cytokines and growth factors in the kidney during the acute disease. Results of the histological and immunohistological studies of eight kidney biopsies show mild to moderate interstitial infiltration of lymphocytes, plasma cells, monocytes/macrophages, and polymorphonuclear leukocytes, mainly eosinophilic granulocytes and neutrophils. An increased expression of the cytokines tumor necrosis factor-alpha, transforming growth factor-beta% and platelet-derived growth factor was seen at the same sites mainly in the peritubular area of the distal nephron. Concomitantly also at the same locations expression of the endothelial adhesion molecules ICAM-1, **VCAM**, and PECAM was seen. Light microscopic changes in tubuli were common. Interestingly, despite the often massive transient proteinuria, no marked changes were seen in the glomeruli of NE kidneys. No evidence of Puumala virus was found in the kidney biopsies.

L2 ANSWER 16 OF 23 MEDLINE DUPLICATE 6
ACCESSION NUMBER: 96390706 MEDLINE
DOCUMENT NUMBER: 96390706
TITLE: Antioxidant-sensitive regulation of inflammatory-response genes in Kaposi's sarcoma cells.
AUTHOR: Offermann M K; Lin J C; Mar E C; Shaw R; Yang J; Medford R M
CORPORATE SOURCE: Division of Hematology, Oncology, Emory University School of Medicine, Atlanta, Georgia, USA.
CONTRACT NUMBER: RO1CA60345 (NCI)
RO1CA67382 (NCI)
P30AR42687 (NIAMS)
SOURCE: JOURNAL OF ACQUIRED IMMUNE DEFICIENCY SYNDROMES AND HUMAN RETROVIROLOGY, (1996 Sep) 13 (1) 1-11.
Journal code: B7J. ISSN: 1077-9450.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199701
AB Kaposi's sarcoma (KS) is a multifocal vascular lesion characterized by

abnormal proliferation of endothelial-like KS cells linked to a pronounced leukocyte infiltration. KS lesions contain novel **herpes**-like DNA sequences, KSHV, hypothesized to originate from the viral pathogen for KS.

Using cultured KS cells that retain the KSHV sequences, diverse signals, including tumor necrosis factor alpha, interleukin (IL) 1 beta, polyinosinic acid/polycytidylic acid and lipopolysaccharide, induced the expression of the cytokine IL-6 and cellular adhesion molecules involved in leukocyte recruitment, including vascular adhesion molecule 1 (**VCAM**-1) and intercellular adhesion molecule 1 (ICAM-1). The thiol-antioxidant pyrrolidine dithiocarbamate (PDTC) selectively inhibited > 90% of the activation of nuclear factor kappa B-like DNA binding activity in KS cells. PDTC also reduced by > 85% induced levels of **VCAM**-1 and IL-6 at the mRNA, protein, and functional levels in KS cells. In contrast, PDTC did not inhibit the induced expression of either ICAM-1 or E-selectin. These studies show that PDTC differentially modulates the expression of inflammatory response genes in KS cells that contain KSHV, suggesting that reduction-oxidation-sensitive events are involved in the regulation of these genes. These studies also suggest that thiol-antioxidants such as PDTC may play a potentially therapeutic role in the treatment of KS by preventing induction of specific inflammatory response genes that may be involved in the pathogenesis of KS.

L2 ANSWER 17 OF 23 MEDLINE DUPLICATE 7
ACCESSION NUMBER: 95115144 MEDLINE
DOCUMENT NUMBER: 95115144
TITLE: Immunopathogenic role of T-cell subsets in **Borna** disease virus-induced progressive encephalitis.
AUTHOR: Planz O; Bilzer T; Stitz L
CORPORATE SOURCE: Institut fur Virologie, Justus-Liebig-Universitat, Giessen, Germany.
SOURCE: JOURNAL OF VIROLOGY, (1995 Feb) 69 (2) 896-903.
Journal code: KCV. ISSN: 0022-538X.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals; Cancer Journals
ENTRY MONTH: 199504

AB **Borna** disease is an immunopathological virus-induced encephalopathy comprising severe inflammation and degenerative brain cell lesions which results in organ atrophy and chronic debility in rats. CD4+ and CD8+ T cells have been reported to be involved in the development of this disease of the central nervous system. A virus-specific homogeneous T-cell line, established in vitro after immunization of rats with the recombinant 24-kDa virus-specific protein, showed antigen-specific proliferation in the presence of the 24-kDa but not the 38-kDa **Borna** disease virus-specific protein, another major virus-specific antigen. This T-cell line, P205, was found to exhibit characteristics of a T-helper cell: CD4+ CD8- IL-2- IL-4- IFN-gamma+ IL-6+ IL-10+. Furthermore, this T-cell line expressed the alpha/beta T-cell receptor and the alpha 4 integrin (**VLA**-4). Adoptive transfer of this helper cell resulted in an increase of antibody titers and two different types of disease in virus-infected rats after cyclophosphamide-induced immunosuppression. (i) Rats receiving T cells between 10 and 18 days after treatment with cyclophosphamide showed an acute lymphoproliferative disease in the gut and lungs within 9 days after adoptive transfer and died. (ii) Passive transfer within the first 5 days after immunosuppressive treatment resulted in typical **Borna** disease associated with neurological symptoms such as ataxia and paresis starting 14 to 16 days after transfer.

Immunohistological analysis of the brains of rats with **Borna** disease uniformly revealed the presence of CD8+ T cells in encephalitic lesions in addition to CD4+ cells that were found in the brains of recipients of the virus-specific CD4+ T-cell line, irrespective of whether neurological symptoms developed or not. However, recipient rats treated with antibodies against CD8+ T cells developed neither encephalitis nor disease. Therefore, CD4+ T cells appear to accumulate in the brain and cause perivascular inflammatory lesions which alone obviously do not cause disease. In contrast, the presence of CD8+ cells apparently directly correlates with the development of neurological symptoms.

L2 ANSWER 18 OF 23 CAPLUS COPYRIGHT 2000 ACS
ACCESSION NUMBER: 1994:673849 CAPLUS
DOCUMENT NUMBER: 121:273849
TITLE: Manufacture of antigens in gag protein-based particles using a minimal retroviral expression cassette
INVENTOR(S): Czaplewski, Lloyd George
PATENT ASSIGNEE(S): British Bio-Technology Ltd., UK
SOURCE: PCT Int. Appl., 40 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9420621	A2	19940915	WO 1994-GB281	19940211
WO 9420621	A3	19941013		
W: AU, CA, CN, DE, FI, GB, JP, KR, NO, NZ, RU, UA, US				
RW: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE				
AU 9460063	A1	19940926	AU 1994-60063	19940211
PRIORITY APPLN. INFO.:			GB 1993-4239	19930301
			WO 1994-GB281	19940211

AB An expression cassette using a single promoter to drive expression of a gag-derived sequence from a complex retrovirus including a rev gene, an RRE element and donor and acceptor elements is described for use in the manuf. of retroviral particles presenting antigens for use in vaccines. The construct is arranged to ensure that the promoter is capable of driving expression of both the gag-derived sequence and the rev-like element. The construct does not contain a functional env gene. The construction of a series of such cassettes for the synthesis of tat protein is demonstrated. COS-7 cells co-transfected with one of these constructs and a CAT gene under control of a tat-responsive promoter showed high levels of expression of the CAT gene.

L2 ANSWER 19 OF 23 EMBASE COPYRIGHT 2000 ELSEVIER SCI. B.V.
ACCESSION NUMBER: 93206488 EMBASE
DOCUMENT NUMBER: 1993206488
TITLE: Leukocyte adhesion molecules in diseased corneas.
AUTHOR: Philipp W.; Gottinger W.
CORPORATE SOURCE: Department of Ophthalmology, University of Innsbruck, Anichstrasse 35,A-6020 Innsbruck, Austria
SOURCE: Investigative Ophthalmology and Visual Science, (1993) 34/8 (2449-2459).
ISSN: 0146-0404 CODEN: IOVSDA
COUNTRY: United States
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 012 Ophthalmology
026 Immunology, Serology and Transplantation
037 Drug Literature Index
LANGUAGE: English

SUMMARY LANGUAGE: English

AB Purpose. To help define the possible role of leukocyte adhesion molecules in the pathogenesis of corneal inflammation, we investigated the presence and distribution of intercellular adhesion molecule-I (ICAM-1), E-selectin (endothelial leukocyte adhesion molecule-1 [ELAM-1]), and vascular cell adhesion molecule-1 (**VCAM**-1) in various corneal diseases. Methods. Monoclonal antibodies (mAbs) to ICAM-1, E-selectin, and **VCAM**-1 were used or immunohistochemical staining of frozen sections of 55 human corneas with various inflammatory and degenerative diseases.'''''''' In addition, we used a panel of mAbs to characterize the composition and density of the inflammatory infiltrates in the diseased corneas. Results. ICAM-1 was focally expressed on epithelial cells in corneas with chronic allograft rejection, herpetic stromal keratitis, zoster keratitis, chemical burns, atopic keratitis, fungal keratitis, and bacterial keratitis. Furthermore, the expression of ICAM-1 was focally increased on keratocytes, corneal endothelial cells, and vascular endothelial cells (particularly at the site of lymphoid infiltration) in these corneas. E-selectin was present on vascular endothelial cells of limbal vessels in corneas with bacterial keratitis and also on endothelial cells of vessels in the stroma of several corneas with chronic inflammatory diseases. **VCAM**-1 was focally expressed on endothelial cells of vessels in the stroma of some corneas with chronic allograft rejection, herpetic stromal keratitis, chemical burns, and atopic keratitis. Interestingly, **VCAM**-1 was also found on inflammatory cells of the macrophage-monocyte lineage in inflamed corneas. Conclusions. Our results demonstrate that ICAM-1, E-selectin, and **VCAM**-1 are expressed in diseased corneas, often in areas of inflammation.

L2 ANSWER 20 OF 23 MEDLINE DUPLICATE 8

ACCESSION NUMBER: 91334433 MEDLINE
DOCUMENT NUMBER: 91334433
TITLE: Identification of a monocyte receptor on herpesvirus-infected endothelial cells.
AUTHOR: Etingin O R; Silverstein R L; Hajjar D P
CORPORATE SOURCE: Department of Medicine, Cornell University Medical College, New York, NY 10021.
CONTRACT NUMBER: HL01687 (NHLBI)
HL46403 (NHLBI)
HL18828 (NHLBI)
+
SOURCE: PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF THE UNITED STATES OF AMERICA, (1991 Aug 15) 88 (16) 7200-3.
Journal code: PV3. ISSN: 0027-8424.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals; Cancer Journals
ENTRY MONTH: 199111

AB The adhesion of circulating blood cells to vascular endothelium may be an initial step in atherosclerosis, inflammation, and wound healing. One mechanism for promoting cell-cell adhesion involves the expression of adhesion molecules on the surface of the target cell. **Herpes** simplex virus infection of endothelium induces arterial injury and has been implicated in the development of human atherosclerosis. We now demonstrate that HSV-infected endothelial cells express the adhesion molecule GMP140 and that this requires cell surface expression of HSV glycoprotein C and local thrombin generation. Monocyte adhesion to HSV-infected endothelial cells was completely inhibited by anti-GMP140 antibodies but not by antibodies to other adhesion molecules such as **VCAM** and ELAM-1. The induction of GMP140 expression on

HSV-infected endothelium may be an important pathophysiological mechanism in virus-induced cell injury and inflammation.

L2 ANSWER 21 OF 23 BIOSIS COPYRIGHT 2000 BIOSIS
ACCESSION NUMBER: 1984:278620 BIOSIS
DOCUMENT NUMBER: BA78:15100
TITLE: ANTIBODIES TO THE HEMORRHAGIC FEVER WITH RENAL SYNDROME VIRUS IN THE HUMAN POPULATIONS OF EUROPEAN RUSSIAN-SFSR AS DETECTED BY RADIO IMMUNOASSAY.
AUTHOR(S): MYASNIKOV Y A; REZAPKIN G V; SHUIKOVA Z V; TKACHENKO E A; IVANOVA A A; NURGALEEVA R G; STEPANENKO A G; VERESHCHAGIN N
N; LOGINOV A I; ET AL
CORPORATE SOURCE: THE INST. OF POLIOMYELITIS AND VIRAL ENCEPHALITIDES, 142782
MOSCOW, U.S.S.R.
SOURCE: ARCH VIROL, (1984) 79 (1-2), 109-116.
CODEN: ARVIDF. ISSN: 0304-8608.
FILE SEGMENT: BA; OLD
LANGUAGE: English
AB Natural immunity to the causative agent of hemorrhagic fever with renal syndrome (HFRS) has first been studied using radioimmunoassay (RIA) in the human population of the Bashkir ASSR with the highest incidence of this infection and of 5 other regions of the RSFSR with lower incidence of HFRS. The antigen was prepared as a suspension of lungs of rodent from natural HFRS foci and contained a high concentration of virus protein. Sera 12,000 from the population of 6 areas of the RSFSR were examined. In the Bashkir ASSR antibodies were detected in 13.7% of the subjects examined, this figure varying in different districts from 4.0 to 41.5% . In the other areas the portion of immune subjects varied from 6.7% in Kuybyshev region to 1.6% in **Vladimir** region. No correlation between the size of the immune portion of the population and average incidence rates for 5 yr was observed. In Bashkiriya, immunity was found in 14.9% of men and 11.8% of women. In other regions, the percent of women with antibodies to HFRS virus was also lower. In the under 40 age-group the percentage of immunity was lower (11.4%) than in older age groups (17.4%). The portion of immune subjects varied in different occupation groups. In HFRS convalescents the antibody was found to persist in high titer for 20 yr (the observation period).

L2 ANSWER 22 OF 23 MEDLINE
ACCESSION NUMBER: 82087072 MEDLINE
DOCUMENT NUMBER: 82087072
TITLE: [Control of the major communicable diseases in the Armenian SSR during the Soviet period].
Itogi bor'by s vazhneishimi infektsionnymi bolezniami v Armianskoi SSR za gody Sovetskoi **vlasti**.
AUTHOR: Dekhtsunian K M
SOURCE: ZHURNAL MIKROBIOLOGII, EPIDEMIOLOGII I IMMUNOBIOLOGII, (1981) (8) 3-8. Ref: 35
Journal code: Y9O. ISSN: 0049-8726.
PUB. COUNTRY: USSR
Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
LANGUAGE: Russian
FILE SEGMENT: Priority Journals
ENTRY MONTH: 198204

L2 ANSWER 23 OF 23 MEDLINE
ACCESSION NUMBER: 74089797 MEDLINE
DOCUMENT NUMBER: 74089797
TITLE: [Clinical forms of the acute period of epidemic encephalitis from the Nervous Diseases Clinic of the

Vladivostok Medical Institute].
Klinicheskie formy ostrogo perioda epidemicheskogo entsefalita (po materialam kliniki nervnykh boleznei **Vladivostokskogo** meditsinskogo instituta.

AUTHOR: Legkonogov V A; Bezrukova L V
SOURCE: ZHURNAL NEVROPATOLOGII I PSIKHIATRII IMENI S. S. KORSAKOVA,
(1973) 73 (2) 185-8.
Journal code: Y9Y. ISSN: 0044-4588.
PUB. COUNTRY: USSR
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: Russian
FILE SEGMENT: Priority Journals
ENTRY MONTH: 197405

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*File 357: Derwent changes DialUnit pricing from May 1, 1999.  See
HELP DERWENT for details.
  File 358:Current BioTech Abs  1983-1999/Dec
         (c) 1999 Royal Soc Chem & DECHEMA
  File 370:Science  1996-1999/Jul W3
         (c) 1999 AAAS
  File 434:SciSearch(R) Cited Ref Sci  1974-1989/Dec
         (c) 1998 Inst for Sci Info

      Set  Items  Description
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? s (vla(w)4) and herpes and (encephalitis or encephalomyelitis)

Processing
Processed  10 of  19 files ...
Completed processing all files
          14111  VLA
        6008786  4
           4010  VLA(W)4
         108578  HERPES
          45321  ENCEPHALITIS
          28202  ENCEPHALOMYELITIS
      S1      0  (VLA(W)4) AND HERPES AND (ENCEPHALITIS OR
                 ENCEPHALOMYELITIS)
? s (vla? or vcam?) and herpes and (encephalitis or encephalomyelitis)

          27147  VLA?
           8587  VCAM?
         108578  HERPES
          45321  ENCEPHALITIS
          28202  ENCEPHALOMYELITIS
      S2      1  (VLA? OR VCAM?) AND HERPES AND (ENCEPHALITIS OR
                 ENCEPHALOMYELITIS)
? t s2/7/all

>>>Format 7 is not valid in file 143

 2/7/1     (Item 1 from file: 34)
DIALOG(R)File  34:SCISEARCH(R) CITED REF SCI
(c) 1999 INST FOR SCI INFO. All rts. reserv.

03078057   Genuine Article#: BZ69J   Number of References: 514
Title: PATHOGENESIS OF VIRUS-INDUCED DEMYELINATION
Author(s): FAZAKERLEY JK; BUCHMEIER MJ
Corporate Source: UNIV CAMBRIDGE,DEPT PATHOL/CAMBRIDGE CB2 1QP//ENGLAND/;
    SCRIPPS CLIN & RES INST,DEPT NEUROPHARMACOL,DIVVIROL/LA JOLLA//CA/00000
Journal: ADVANCES IN VIRUS RESEARCH, 1993, V42, P249-324
ISSN: 0065-3527
Language: ENGLISH   Document Type: REVIEW
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 s (vla? or vcam?) and herpes and (encephalitis or encephalomyelitis)

           27147  VLA?
            8587  VCAM?
          108578  HERPES
           45321  ENCEPHALITIS
           28202  ENCEPHALOMYELITIS
      S2       1  (VLA? OR VCAM?) AND HERPES AND (ENCEPHALITIS OR
                  ENCEPHALOMYELITIS)
? t s2/7/all

>>>Format 7 is not valid in file 143

 2/7/1     (Item 1 from file: 34)
DIALOG(R)File  34:SCISEARCH(R) CITED REF SCI
(c) 1999 INST FOR SCI INFO. All rts. reserv.

03078057   Genuine Article#: BZ69J   Number of References: 514
Title: PATHOGENESIS OF VIRUS-INDUCED DEMYELINATION
Author(s): FAZAKERLEY JK; BUCHMEIER MJ
Corporate Source: UNIV CAMBRIDGE,DEPT PATHOL/CAMBRIDGE CB2 1QP//ENGLAND/;
    SCRIPPS CLIN & RES INST,DEPT NEUROPHARMACOL,DIVVIROL/LA JOLLA//CA/00000
Journal: ADVANCES IN VIRUS RESEARCH, 1993, V42, P249-324
ISSN: 0065-3527
Language: ENGLISH   Document Type: REVIEW
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2/8/1 (Item 1 from file: 34)
DIALOG(R)File 34:(c) 1999 INST FOR SCI INFO. All rts. reserv.

03078057 Genuine Article#: BZ69J Number of References: 514
Title: PATHOGENESIS OF VIRUS-INDUCED DEMYELINATION
Journal Subject Category: VIROLOGY
Identifiers--KeyWords Plus: CENTRAL-NERVOUS-SYSTEM; SEMLIKI-FOREST VIRUS; MURINE **ENCEPHALOMYELITIS** VIRUS; **HERPES**-SIMPLEX VIRUS; MYELIN BASIC-PROTEIN; EXPERIMENTAL ALLERGIC **ENCEPHALOMYELITIS**; MOUSE HEPATITIS-VIRUS; HUMAN-IMMUNODEFICIENCY-VIRUS; SUBACUTE SCLEROSING PANENCEPHALITIS; CANINE-DISTEMPER VIRUS
Research Fronts: 92-2091 006 (TOXOPLASMIC **ENCEPHALITIS** IN AIDS; HIV-1 INFECTION; NEUROPSYCHOLOGICAL PERFORMANCE; COGNITIVE IMPAIRMENT; CENTRAL-NERVOUS-SYSTEM MANIFESTATIONS)
92-3171 005 (CULTURED RAT MICROGLIA; BRAIN MACROPHAGES; INTERLEUKIN-1-BETA INDUCTION OF TUMOR-NECROSIS-FACTOR-ALPHA GENE-EXPRESSION; INFLAMMATORY CYTOKINES)
92-2572 003 (OLIGODENDROCYTE LINEAGE; INVITRO DIFFERENTIATION OF GLIAL PROGENITOR CELLS; BASIC FIBROBLAST GROWTH-FACTOR; RAT CNS CULTURES; TYPE-2 ASTROCYTE)
92-0871 002 (HUMAN T-CELL LYMPHOTROPIC VIRUS TYPE-I; INVITRO INFECTION; SURFACE PROTEIN)
92-2403 002 (HUMAN-IMMUNODEFICIENCY-VIRUS TYPE-1; ENVELOPE V3 LOOP; PRINCIPAL NEUTRALIZATION DETERMINANT; CD4 BINDING-SITE; GP120 DISSOCIATION)
92-0741 001 (ADHESION MOLECULES; REGULATION OF THE **VLA** INTEGRIN LIGAND INTERACTIONS; LFA-1 AVIDITY IN HUMAN B-CELLS; COSTIMULATORY SIGNAL)
92-0821 001 (EPSTEIN-BARR-VIRUS INFECTION; INSITU HYBRIDIZATION; POSTTRANSPLANT LYMPHOPROLIFERATIVE DISORDERS)
92-1747 001 (TRANSFERRIN IN THE HUMAN BRAIN; IRON UPTAKE; TRANSENDOTHELIAL TRANSPORT; TISSUES OF RATS; RETINAL ENDOTHELIUM INVITRO)
92-2354 001 (PROGRESSIVE MULTIFOCAL LEUKOENCEPHALOPATHY; JC VIRUS; STEREOTAXIC BRAIN BIOPSY)
92-6544 001 (HEPATITIS-C VIRUS; RNA RECOMBINATION; DEFECTIVE VIRAL PARTICLES; RAPID SEQUENCE EVOLUTION)
92-7639 001 (TUMOR-NECROSIS-FACTOR-ALPHA STIMULATES EXPRESSION; MURINE MACROPHAGES; VIRAL GENES; ANTIVIRAL ACTIVITY)

2/9/1 (Item 1 from file: 34)
DIALOG(R)File 34:SCISEARCH(R) CITED REF SCI

03078057 Genuine Article#: BZ69J Number of References: 514
Title: PATHOGENESIS OF VIRUS-INDUCED DEMYELINATION
Author(s): FAZAKERLEY JK; BUCHMEIER MJ
Corporate Source: UNIV CAMBRIDGE,DEPT PATHOL/CAMBRIDGE CB2 1QP//ENGLAND/;
SCRIPPS CLIN & RES INST,DEPT NEUROPHARMACOL,DIVVIROL/LA JOLLA//CA/00000
Journal: ADVANCES IN VIRUS RESEARCH, 1993, V42, P249-324
ISSN: 0065-3527
Language: ENGLISH Document Type: REVIEW
Geographic Location: ENGLAND; USA
Subfile: SciSearch
Journal Subject Category: VIROLOGY
Identifiers--KeyWords Plus: CENTRAL-NERVOUS-SYSTEM; SEMLIKI-FOREST VIRUS;
MURINE **ENCEPHALOMYELITIS** VIRUS; **HERPES**-SIMPLEX VIRUS;
MYELIN BASIC-PROTEIN; EXPERIMENTAL ALLERGIC **ENCEPHALOMYELITIS**;
MOUSE HEPATITIS-VIRUS; HUMAN-IMMUNODEFICIENCY-VIRUS; SUBACUTE
SCLEROSING PANENCEPHALITIS; CANINE-DISTEMPER VIRUS
Research Fronts: 92-2091 006 (TOXOPLASMIC **ENCEPHALITIS** IN AIDS;
HIV-1 INFECTION; NEUROPSYCHOLOGICAL PERFORMANCE; COGNITIVE IMPAIRMENT;
CENTRAL-NERVOUS-SYSTEM MANIFESTATIONS)
92-3171 005 (CULTURED RAT MICROGLIA; BRAIN MACROPHAGES;
INTERLEUKIN-1-BETA INDUCTION OF TUMOR-NECROSIS-FACTOR-ALPHA
GENE-EXPRESSION; INFLAMMATORY CYTOKINES)
92-2572 003 (OLIGODENDROCYTE LINEAGE; INVITRO DIFFERENTIATION OF GLIAL
PROGENITOR CELLS; BASIC FIBROBLAST GROWTH-FACTOR; RAT CNS CULTURES;
TYPE-2 ASTROCYTE)
92-0871 002 (HUMAN T-CELL LYMPHOTROPIC VIRUS TYPE-I; INVITRO INFECTION;
SURFACE PROTEIN)
92-2403 002 (HUMAN-IMMUNODEFICIENCY-VIRUS TYPE-1; ENVELOPE V3 LOOP;
PRINCIPAL NEUTRALIZATION DETERMINANT; CD4 BINDING-SITE; GP120
DISSOCIATION)
92-0741 001 (ADHESION MOLECULES; REGULATION OF THE **VLA** INTEGRIN
LIGAND INTERACTIONS; LFA-1 AVIDITY IN HUMAN B-CELLS; COSTIMULATORY
SIGNAL)
92-0821 001 (EPSTEIN-BARR-VIRUS INFECTION; INSITU HYBRIDIZATION;
POSTTRANSPLANT LYMPHOPROLIFERATIVE DISORDERS)
92-1747 001 (TRANSFERRIN IN THE HUMAN BRAIN; IRON UPTAKE;
TRANSENDOTHELIAL TRANSPORT; TISSUES OF RATS; RETINAL ENDOTHELIUM
INVITRO)
92-2354 001 (PROGRESSIVE MULTIFOCAL LEUKOENCEPHALOPATHY; JC VIRUS;
STEREOTAXIC BRAIN BIOPSY)
92-6544 001 (HEPATITIS-C VIRUS; RNA RECOMBINATION; DEFECTIVE VIRAL
PARTICLES; RAPID SEQUENCE EVOLUTION)
92-7639 001 (TUMOR-NECROSIS-FACTOR-ALPHA STIMULATES EXPRESSION; MURINE
MACROPHAGES; VIRAL GENES; ANTIVIRAL ACTIVITY)

=> t l2 ibib abs tot

L2 ANSWER 1 OF 1 MEDLINE DUPLICATE 1
ACCESSION NUMBER: 1998180905 MEDLINE
DOCUMENT NUMBER: 98180905
TITLE: Evidence for deficiencies in intracerebral cytokine production, adhesion molecule induction, and T cell recruitment in **herpes** simplex virus type-2 infected mice.
AUTHOR: Lewandowski G; Hobbs M V
CORPORATE SOURCE: Department of Neuropharmacology, The Scripps Research Institute, La Jolla, CA 92037, USA.
CONTRACT NUMBER: R29MH51926 (NIMH)
AG09822 (NIA)
SOURCE: JOURNAL OF NEUROIMMUNOLOGY, (1998 Jan) 81 (1-2) 58-65.
Journal code: HSO. ISSN: 0165-5728.
PUB. COUNTRY: Netherlands
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199806
ENTRY WEEK: 19980603
AB We examined the intracerebral T cell response in mice infected with neurovirulent HSV-2 strains and an avirulent HSV-1. In HSV-2-infected brains, (i) IL-1beta, TNF-alpha and IFN-gamma mRNA expression was low, (ii) ICAM-1 and **VCAM**-1 were not induced, (iii) few CD4+ or CD8+ cells were detected. By contrast, in HSV-1-infected brains, (i) cytokine mRNA expression was high, (ii) adhesion molecules were strongly expressed,
(iii) many T cells were detected. We suggest that deficient T cell extravasation into HSV-2-infected brain regions is caused by negligible ICAM-1 and **VCAM**-1 expression, which is due to low expression of

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FILE COVERS 1967 - 23 Jul 2000 VOL 133 ISS 5
FILE LAST UPDATED: 21 Jul 2000 (20000721/ED)

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=> s (vla? or vcam?) and herpes and encephalitis

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          4877 VLA?
          2460 VCAM?
         17768 HERPES
          3503 ENCEPHALITIS
L3           0 (VLA? OR VCAM?) AND HERPES AND ENCEPHALITIS
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is

(FILE 'HOME' ENTERED AT 10:08:40 ON 23 JUL 2000)

FILE 'MEDLINE, BIOSIS, EMBASE, CAPLUS' ENTERED AT 10:09:09 ON 23 JUL 2000
L1 17 S RUBIN, STEPHEN OR RUBIN STEPHEN/AU
L2 16 DUP REM L1 (1 DUPLICATE REMOVED)
L3 0 S L2 AND ENCEPHALITIS
L4 24 S YEDNOCK, TED OR YEDNOCK TED /AU
L5 16 DUP REM L2 (0 DUPLICATES REMOVED)
L6 0 S L5 AND ENCEPHALITIS

=> s encephalitis and herpes

L7 7026 ENCEPHALITIS AND HERPES

=> s encephalitis and herpes and (inhibit? or suppress)(P)(T(w)cell? or t(w)lymphocyt?)

2 FILES SEARCHED...
3 FILES SEARCHED...
L8 9 ENCEPHALITIS AND HERPES AND (INHIBIT? OR SUPPRESS)(P)(T(W) CELL?
OR T(W) LYMPHOCYT?)

=> dup rem

ENTER L# LIST OR (END):18

PROCESSING COMPLETED FOR L8
L9 6 DUP REM L8 (3 DUPLICATES REMOVED)

=> t 19 ibib abs tot

L9 ANSWER 1 OF 6 MEDLINE DUPLICATE 1
ACCESSION NUMBER: 2000015188 MEDLINE
DOCUMENT NUMBER: 20015188
TITLE: Chronic brain inflammation and persistent **herpes** simplex virus 1 thymidine kinase expression in survivors of syngeneic glioma treated by adenovirus-mediated gene therapy: implications for clinical trials.
AUTHOR: Dewey R A; Morrissey G; Cowsill C M; Stone D; Bolognani F; Dodd N J; Southgate T D; Klatzmann D; Lassmann H; Castro M G; Lowenstein P R
CORPORATE SOURCE: Department of Neuropathology, Institute of Psychiatry, Kings College London, DeCrespigny Park, Denmark Hill, London SE5 8AS, UK.
SOURCE: NATURE MEDICINE, (1999 Nov) 5 (11) 1256-63. Journal code: CG5. ISSN: 1078-8956.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200001
ENTRY WEEK: 20000104
AB The long-term consequences of adenovirus-mediated conditional cytotoxic gene therapy for gliomas remain uncharacterized. We report here detection

of active brain inflammation 3 months after successful **inhibition** of syngeneic glioma growth. The inflammatory infiltrate consisted of activated macrophages/microglia and astrocytes, and **T lymphocytes** positive for leucosyalin, CD3 and CD8, and included secondary demyelination. We detected strong widespread **herpes** simplex virus 1 thymidine kinase immunoreactivity and vector genomes throughout large areas of the brain. Thus, patient evaluation and the design of clinical trials in ongoing and future gene therapy for brain glioblastoma must address not only tumor-killing efficiency, but also long-term active brain inflammation, loss of myelin fibers and persistent transgene expression.

L9 ANSWER 2 OF 6 CAPLUS COPYRIGHT 2000 ACS
ACCESSION NUMBER: 1996:128017 CAPLUS
DOCUMENT NUMBER: 124:194289
TITLE: Cage compounds, their preparation and use as antiviral agents
INVENTOR(S): Marcuccio, Sebastian Mario; Turner, Kathleen Anne; Holan, George; Osvath, Peter; Sargeson, Alan Mcleod; Weigold, Helmut; Geue, Rodney
PATENT ASSIGNEE(S): Commonwealth Scientific and Industrial Research, Australia
SOURCE: PCT Int. Appl., 58 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9531202	A1	19951123	WO 1995-AU283	19950517
W: AM, AT, AU, BB, BG, BR, BY, CA, CH, CN, CZ, DE, DK, EE, ES, FI, GB, GE, HU, IS, JP, KE, KG, KP, KR, KZ, LK, LR, LT, LU, LV, MD, MG, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, TJ, TM, TT				
RW: KE, MW, SD, SZ, UG, AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG				
AU 9524397	A1	19951205	AU 1995-24397	19950517
ZA 9504017	A	19960117	ZA 1995-4017	19950517
PRIORITY APPLN. INFO.:			AU 1994-5656	19940517
			AU 1994-5720	19940519
			WO 1995-AU283	19950517

OTHER SOURCE(S): CASREACT 124:194289; MARPAT 124:194289
GI For diagram(s), see printed CA Issue.
AB A method of treatment and/or prophylaxis of a viral infection comprises administration of a cage compd. [I; M = metal capable of forming hexacoordinate complexes; p = 1-6; m, n = 0, 1; A1-A6 = NH, N, O, S; R1, R2 = H, halo, NO2, CN, (substituted) alkyl, OH, (substituted) alkoxy, (substituted) amino, etc.; other positions may be variously substituted]. I are prepd. by reacting a metal complex having .gtoreq.3 terminal NH2 groups with HCHO, a base, and a nucleophile optionally contg. a functional group which may react with any coordinated amine also present on the metal complex, leading to encapsulation and formation of a cage mol. Thus, Co complex II [X = Me; Y = (C8H17)2N(CH2)2NH] showed an ED50 of 0.53 .mu.M against HIV-1 in MT-4 cells in vitro, and 3 .mu.M against duck hepatitis B virus in primary duck hepatocyte cultures. The compds. were nontoxic to mice at .ltoreq.50 mg/kg. [Co(sen)].Cl3 [sen = 5-(4-amino-2-azabutyl)-5-methyl-3,7-diazanonane-1,9-diamine] reacted with paraformaldehyde and n-butanal in MeCN in the presence of NaClO4 to form II (X = Me; Y = Et). Controlled-release tablets were prepd. by wet granulation of active

ingredient 500, hydroxypropylmethylcellulose 112, lactose 53, and povidone
28 mg, followed by addn. of 7 mg Mg stearate and compression.

L9 ANSWER 3 OF 6 MEDLINE DUPLICATE 2
ACCESSION NUMBER: 94118416 MEDLINE
DOCUMENT NUMBER: 94118416
TITLE: Immunization with replication-defective mutants of **herpes** simplex virus type 1: sites of immune intervention in pathogenesis of challenge virus infection.
AUTHOR: Morrison L A; Knipe D M
CORPORATE SOURCE: Department of Microbiology and Molecular Genetics, Harvard Medical School, Boston, Massachusetts 02115..
CONTRACT NUMBER: PO1 AI 24010 (NIAID)
SOURCE: JOURNAL OF VIROLOGY, (1994 Feb) 68 (2) 689-96.
Journal code: KCV. ISSN: 0022-538X.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals; Cancer Journals
ENTRY MONTH: 199404
AB Replication-defective mutants of **herpes** simplex virus type 1 (HSV-1) were used as a new means to immunize mice against HSV-1-mediated ocular infection and disease. The effects of the induced immune responses on pathogenesis of acute and latent infection by challenge virus were investigated after corneal inoculation of immunized mice with virulent HSV-1. A single subcutaneous injection of replication-defective mutant virus protected mice against development of **encephalitis** and keratitis. Replication of the challenge virus at the initial site of infection was lower in mice immunized with attenuated, wild-type parental virus (KOS1.1) or replication-defective mutant virus than in mice immunized with uninfected cell extract or UV-inactivated wild-type virus. Significantly, latent infection in the trigeminal ganglia was reduced in mice given one immunization with replication-defective mutant virus and was completely prevented by two immunizations. Acute replication in the trigeminal ganglia was also prevented in mice immunized twice with wild-type or mutant virus. The level of protection against infection and disease generated by immunization with replication-defective mutant viruses was comparable to that of infectious wild-type virus in all cases.
In addition, **T-cell** proliferative and neutralizing antibody responses following immunization and corneal challenge were of similar strength in mice immunized with replication-defective mutant viruses or with wild-type virus. Thus, protein expression by forms of HSV-1 capable of only partially completing the replication cycle can induce an immune response in mice that efficiently decreases primary replication of virulent challenge virus, interferes with acute and latent infection of the nervous system, and **inhibits** the development of both keratitis and systemic neurologic disease.

L9 ANSWER 4 OF 6 BIOSIS COPYRIGHT 2000 BIOSIS
ACCESSION NUMBER: 1993:524687 BIOSIS
DOCUMENT NUMBER: PREV199396138094
TITLE: HIV-1 gp41 binds to several proteins on the human B-cell line, Raji.
AUTHOR(S): Chen, Ying-Hua; Bock, Guenther; Vornhagen, Rolf; Steindl, Franz; Katinger, Hermann; Dierich, Manfred P. (1)
CORPORATE SOURCE: (1) Inst. Hygiene, Fritz-Pregl-Strasse 3, 6010 Innsbruck Austria
SOURCE: Molecular Immunology, (1993) Vol. 30, No. 13, pp. 1159-1163.
ISSN: 0161-5890.
DOCUMENT TYPE: Article
LANGUAGE: English
AB Based on our findings that HIV-1 gp41 independently of CD4, can bind to

the helper **T-cell** line H9, we characterized putative binding of HIV-1 gp41 to B-cell lines, Raji, Bjab and Ramos. Using fluorescence-activated cell sorter (FACS) we examined the binding of soluble gp41 (sgp41; Env amino acid 539-684) to these B-cell lines. Using sgp41 attached to sepharose beads Raji cell lysates were absorbed. The sgp41-eluate of Raji cell lysates could **inhibit** the sgp41-binding to Raji cells. By SDS-PAGE of sgp41-eluate of Raji cell lysates four strong protein band, 37, 45, 49 and 62 kD, and a weak band of 92 kD were stained with Coomassie blue. By Western blot (ligand blot) analysis using sgp41 four protein bands, 37, 45, 49 and 62 kD, were observed in sgp41-eluate of Raji cell lysates. To test the individual proteins the five proteins were isolated from the sgp41-eluate of Raji cell lysates. Three proteins, 45, 49 and 62 kD, each could partially **inhibit** the sgp41-binding to Raji cells. The results suggest that these three proteins in Raji cell lysates are possible candidates for the putative gp41 receptor(s).

L9 ANSWER 5 OF 6 MEDLINE
ACCESSION NUMBER: 83199906 MEDLINE
DOCUMENT NUMBER: 83199906
TITLE: [Mechanism of virus-induced immunopathology. I. The reactivity of immunocompetent cells in acute herpetic infection in an experiment].
O mekhanizme virusindutsirovannoi immunopatologii. Soobshchenie I. Reaktivnost' immunokompetentnykh kletok pri ostroi gerpeticheskoi infektsii v eksperimente.
AUTHOR: Shavrova E N; Sharko R M; Khliustov S V
SOURCE: ZHURNAL MIKROBIOLOGII, EPIDEMIOLOGII I IMMUNOBIOLOGII, (1983 Mar) (3) 65-8.
Journal code: Y9O. ISSN: 0372-9311.
PUB. COUNTRY: USSR
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: Russian
FILE SEGMENT: Priority Journals
ENTRY MONTH: 198308
AB The state of general and specific responsiveness of thymocytes and splenocytes in non-inbred white mice has been studied in the reaction of lymphocyte blast transformation under the influence of phytohemagglutinin (PHA) and **herpes** simplex virus. Experimental herpetic **encephalitis** has been shown to give rise to the development of pronounced immunosuppression, which is confirmed by a considerable decrease (P less than 0.05) in the levels of the PHA- and virus-induced transformation of thymocytes and splenocytes in infected mice in comparison with the similar transformation characteristics of intact lymphocytes. The **inhibition** of the general and specific responsiveness of **T-lymphocytes** has been found to be one of the possible mechanisms of immunosuppression in acute **herpes** infection.

L9 ANSWER 6 OF 6 EMBASE COPYRIGHT 2000 ELSEVIER SCI. B.V.
ACCESSION NUMBER: 82220024 EMBASE
DOCUMENT NUMBER: 1982220024
TITLE: The effect of human gammaglobulin derivatives on human lymphoblastoid cell lines persistently infected with **herpes** simplex virus.
AUTHOR: Arita K.; Yamauchi E.; Maki S.; Kato S.
CORPORATE SOURCE: Dept. Pathol., Res. Inst. Microb. Dis., Osaka Univ., Osaka, Japan
SOURCE: Acta Paediatrica Japonica (Overseas Edition), (1981) 23/2 (201-207).
CODEN: APDJBE
COUNTRY: Japan
DOCUMENT TYPE: Journal

FILE SEGMENT: 026 Immunology, Serology and Transplantation
047 Virology
007 Pediatrics and Pediatric Surgery
LANGUAGE: English

AB Human lymphoblastoid cells (NC-37) were infected with two strains of **herpes** simplex virus type 1 (HSV-1). Persistent infections with no strains (a freshly isolated strain, Seike strain, and Miyama strain) of HSV-1 were established in NC-37 cells. In NC-37 cells infected with HSV-1 (Seike), the growth of cells was **inhibited**, 6-72% of viable cells were positive for HSV-antigen by fluorescent antibody technique, and the percentage of HSV-antigen positive cells seemed to be inversely related to that of viable cells. Growth of cells and infectious viruses was seen for more than 396 days without external support. NC-37 cells infected with HSV-1 were subcultured with fresh medium containing human gammaglobulin derivatives. The percentage of HSV-antigen positive cells decreased and no infectious viruses were detected in the treated cells and culture fluids after more than 16 days. It is thought that HSV continues to associate with **T-lymphocytes** stimulated in vivo for a long period of time after the appearance of circulating antibody, at least for two weeks, and lymphocytes persistently infected with HSV have a relation to the pathogenesis of herpesvirus **encephalitis** in older children and adults similar to the pathogenesis of SSPE.

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=> e yednock/in

E#      FILE            FREQUENCY  TERM
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E1      USPAT                2     YEDNASTY, JOSEPH S/IN
E2      USPAT                1     YEDNICK, THEODORE A/IN
E3      USPAT                0 --> YEDNOCK/IN
E4      USPAT                1     YEDNOCK, TED/IN
E5      USPAT                3     YEDNOCK, TED A/IN
E6      USPAT                1     YEDNOCK, THEODORE A/IN
E7      USPAT                1     YEDOR, HARRY M/IN
E8      USPAT                2     YEDVAB, JOSEPH/IN
E9      USPAT                1     YEE KWONG, TIMOTHY K/IN
E10     USPAT               16     YEE, ABRAHAM/IN
E11     USPAT                3     YEE, ABRAHAM F/IN
E12     USPAT                1     YEE, AH LYAN/IN

=> s e2-e6

             1 "YEDNICK, THEODORE A"/IN
             0 YEDNOCK/IN
             1 "YEDNOCK, TED"/IN
             3 "YEDNOCK, TED A"/IN
             1 "YEDNOCK, THEODORE A"/IN
L7           6 ("YEDNICK, THEODORE A"/IN OR YEDNOCK/IN OR "YEDNOCK, TED"/I
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=> s l7 and vla(w)4

           343 VLA
       2397640 4
           134 VLA(W)4
L8           2 L7 AND VLA(W)4

=> d l8 1-2


1.  5,840,299, Nov. 24, 1998, Humanized antibodies against leukocyte
adhesion molecule VLA-4; Mary M. Bendig, et al., 424/133.1,
130.1, 141.1, 143.1, 144.1, 153.1, 154.1, 173.1; 435/7.1, 7.2, 7.21,
7.24, 69.6, 320.1; 530/387.3, 388.22, 388.73, 388.75; 536/23.53 [IMAGE
AVAILABLE]

2.  5,260,210, Nov. 9, 1993, Blood-brain barrier model; Lee L. Rubin, et
al., 435/325, 398, 402 [IMAGE AVAILABLE]

=> s l8 and encephalitis

          1375 ENCEPHALITIS
L9           1 L8 AND ENCEPHALITIS

=> d l9 1


1.  5,840,299, Nov. 24, 1998, Humanized antibodies against leukocyte
adhesion molecule VLA-4; Mary M. Bendig, et al., 424/133.1,
130.1, 141.1, 143.1, 144.1, 153.1, 154.1, 173.1; 435/7.1, 7.2, 7.21,
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427.24, 69.6, 320.1; 530/387.3, 388.22, 388.73, 388.75; 536/23.53 [IMAGE AVAILABLE]

DETD(63)

The invention also provides methods of treatment that exploit the capacity of humanized MAb 21.6 to block .alpha.4-dependent interactions of the **VLA-4** receptor. The .alpha.4-dependent interaction of the **VLA-4** receptor with the VCAM-1 ligand on endothelial cells is an early event in many inflammatory responses, including those that include multiple sclerosis (Yednock et al., Nature 356, 63 (1992), Baron et al., J. Exp. Med. 177, 57 (1993)), meningitis, **encephalitis**, stroke, other cerebral traumas, inflammatory bowel disease (Hamann et al., J. Immunol. 152, 3238 (1994)), ulcerative colitis, Crohn's disease, rheumatoid. . .

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 ********
ENTER PASSWORD:
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Welcome to DIALOG

Dialog level 99.05.27D

Last logoff:  12jun99 08:49:08
Logon file001 13jun99 11:38:01
ANNOUNCEMENT    ****    ANNOUNCEMENT    ****    ANNOUNCEMENT
NEW
***UPI News (Files 261 for current news & 861 for archive news)
***Africa News (Files 606 for current news & 806 for archive news)
***ITAR/TASS (Files 607 for current news & 667 for archive news)
***Xinhua News (Files 618 for current news & 818 for archive news)
***Business Wire (Files 610 for current news & 810 for archive news)
***PR Newswire (Files 613 for current news & 813 for archive news)
***U.S. Newswire (Files 605 for current news & 665 for archive news)
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***Irish Times (File 477)
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***Medline (Files 154,155)
***EMBASE (Files 72,73)
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***Toxline (File 156)
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      Set  Items  Description
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? b 410

>>>'IALOG' not recognized as set or accession number
? set hi ;set hi

       13jun99 11:38:08 User208760 Session D1257.1
            $0.27    0.084 DialUnits File1
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     $0.27  Estimated cost File1
            FTSNET   0.016 Hrs.
     $0.27  Estimated cost this search
     $0.27  Estimated total session cost   0.084 DialUnits

File 410:Chronolog(R)  1981-1999 May/Jun
       (c) 1999 The Dialog Corporation plc

      Set  Items  Description
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? begin 55,72,154,399,357

       13jun99 11:38:22 User208760 Session D1257.2
            $0.00    0.041 DialUnits File410
     $0.00  Estimated cost File410
            FTSNET   0.003 Hrs.
     $0.00  Estimated cost this search
     $0.27  Estimated total session cost   0.125 DialUnits

SYSTEM:OS  - DIALOG OneSearch
  File  55:Biosis Preiviews(R)  1993-1999/Jun W2
        (c) 1999 BIOSIS
*File  55: File is reloaded. Accession number changed.
  File  72:EMBASE  1993-1999/May W5
        (c) 1999 Elsevier Science B.V.
*File  72: EMBASE reloaded. Accession numbers have changed.
  File 154:MEDLINE(R)  1993-1999/Aug W1
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  File 399:CA SEARCH(R)  1967-1999/UD=13024
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*File 357: Derwent changes DialUnit pricing from May 1, 1999.  See
HELP DERWENT for details.

      Set  Items  Description
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? s encephalitis and vla(w)4

          14357  ENCEPHALITIS
           4217  VLA
        2042793  4
           2735  VLA(W)4
     S1      32  ENCEPHALITIS AND VLA(W)4
? rd s1

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     S2      19  RD S1 (unique items)
?  s s2 and (arbovirus or herpes)

             19  S2
           3495  ARBOVIRUS
          45737  HERPES
     S3       0  S2 AND (ARBOVIRUS OR HERPES)
? t s2/7/all


 2/7/1     (Item 1 from file: 55)
DIALOG(R)File  55:Biosis Preiviews(R)
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11226032 BIOSIS NO.: 199800007364
Semliki Forest virus infection leads to increased expression of adhesion molecules on splenic T-cells and on brain vascular endothelium.

AUTHOR: Soilu-Hanninen Merja(a); Roytta Matias; Salmi Aimo A; Salonen Reijo
AUTHOR ADDRESS: (a)Turku Immunol. Cent., Univ. Turku, Kiinamyllynkatu 13, FIN-20520 Turku, Finland

JOURNAL: Journal of Neurovirology 3 (5):p350-360 Oct., 1997
ISSN: 1355-0284
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: Semliki Forest virus A7 (SFV-A7) is a neurotropic alphavirus that leads to an asymptomatic **encephalitis** in adult immunocompetent mice. We studied the expression of leukocyte and endothelial cell adhesion molecules in the spleen and in the central nervous system (CNS) during SFV-A7 infection. Kinetics of the expression of LFA-1alpha/CD11a, LFA-1beta/CD18, Mac-1/CD11b, **VLA-4**/CD49d, ICAM-1/CD54 and L-selectin/CD62L was determined on splenic CD4+ and CD8+ T-cells and macrophages by flow cytometry. Time course of the expression of these antigens and VCAM-1/CD106 as well as viral antigens in the CNS was studied by immunoperoxidase staining. In the spleen, a sustained increase in LFA-1 -expression and a temporary increase at day 7 in the expression of **VLA-4**, Mac-1 and ICAM-1 were detected on CD8+ T-cells. L-selectin was downregulated on CD4+ cells. Adhesion molecules on macrophages remained unchanged. In the CNS, expression of Mac-1+, **VLA-4**+ and LFA-1+ cells increased in parallel with the kinetics of the expression of their ligands ICAM-1 and VCAM-1 on brain vessels. Upregulation of adhesion molecules peaked between days 5-8 and was most prominent in the cerebellar and brain stem white matter where viral antigens were most abundant. We conclude that the adhesion molecules profile of splenic T cells is altered during SFV-A7 infection which may influence their homing into the CNS. Macrophages are probably recruited non-specifically as a consequence of activation of the brain vascular endothelium in the inflamed areas of the brain.

2/7/2 (Item 2 from file: 55)
DIALOG(R)File 55:Biosis Preiviews(R)

10386691 BIOSIS NO.: 199699007836
Regulation of lymphocyte homing into the brain during viral **encephalitis** at various stages of infection.

AUTHOR: Irani David N(a); Griffin Diana E
AUTHOR ADDRESS: (a)Dep. Neurol., Johns Hopkins Hosp., Meyer 6-181, 600 N. Wolfe St., Baltimore, MD 21287-7681, USA

JOURNAL: Journal of Immunology 156 (10):p3850-3857 1996
ISSN: 0022-1767
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: The passage of circulating lymphocytes into the central nervous system (CNS) during acute viral **encephalitis** was studied in vivo using fluorescently labeled cells inoculated into Sindbis virus (SV)-infected mice. Donor lymphocytes were detected in the brains of recipient animals when mononuclear cells were isolated from the CNS and screened by flow cytometry. The magnitude of this accumulation related to

the duration of **encephalitis** in recipient mice and to the activation state of the inoculated cells. While Ag specificity did not influence lymphocyte entry into the inflamed CNS at any stage of infection, SV-immune cells were retained selectively within the brains of infected animals compared with cells of an irrelevant specificity. Coincident with the onset of CNS inflammation, ICAM-1 and VCAM-1 were up-regulated on cerebrovascular endothelium. Lymphocyte entry into the brains of infected animals during maximal inflammation could be inhibited by pretreating inoculated cells with Abs that blocked LFA-1, but not with those that blocked **VLA-4** or down-regulated CD44. None of these reagents prevented lymphocyte entry into the brain at the onset of inflammation, suggesting that the earliest recruited cells utilize presently uncharacterized receptor-ligand interactions. These data show that the degree of existing inflammation and the activation state of circulating cells, but not their Ag specificity, influence lymphocyte recruitment into the brain during SV **encephalitis**. While CNS homing can be blocked with Abs against known adhesion molecules during peak inflammation, lymphocyte entry into the brain during early infection remains poorly characterized.

2/7/3 (Item 3 from file: 55)
DIALOG(R)File 55:Biosis Preiviews(R)

10140576 BIOSIS NO.: 199698595494
Dementia and HIV: Neuropathology.

AUTHOR: Seilhean D(a); Duyckaerts C; Hauw J J
AUTHOR ADDRESS: (a)Lab. Neuropathologie R. Escourolle, Hopital Salpetriere, 47, Bd de l'Hopital, F 75651 Paris Cede, France

JOURNAL: Journal of Neuroradiology 22 (3):p161-162 1995
ISSN: 0150-9861
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: French; Non-English
SUMMARY LANGUAGE: French; English

ABSTRACT: Cognitive disorders associated with HIV infection may be due to focal lesions (lymphoma, toxoplasmosis, progressive multifocal leukoencephalitis, etc.), metabolic encephalopathy (e.g. hepatic insufficiency) or psychiatric disorders (depression). In the absence of such causes a cognitive and motor syndrome associated with HIV infection has been defined on clinical criteria (Working group of the American Academy of Neurology, 1991). This syndrome is not consistently associated with any specific lesion. Neither the multifocal **encephalitis** of HIV or CMV infection nor the diffuse leukoencephalopathy associated with HIV are the only causes. The existence of a neocortical neuronal loss has been suggested by several retrospective studies, but our prospective study has not shown cortical or subcortical atrophy. Measurement of neuronal density in Brodmann's areas 4, 9 and 40 has not revealed a significant loss either global. by layer, or by column. The only constant lesion was gliosis of the cortex and white matter. Neuronal loss, therefore, is not indispensable to the occurrence of cognitive disorders in AIDS. The mechanism of dementia might be: - dysfunction of cortical neurons (dendritic abnormalities, virus/neurotransmitter competition): - subcortical dysfunction, as suggested by the high density of microglial nodules in that region: - white matter lesions which could be due to abnormalities in the blood-brain barrier. The expression of cell adhesion molecules (VCAM- 1, **VLA-4**, ICAM- 1 and LFA-1) by endothelial cerebral cells is not significantly different in AIDS patients, demented or not, and in patients with multiple sclerosis. In contrast, the expression of VCAM1- by astrocytes is significantly increased in demented AIDS patients compared with non demented ones. This finding opens new

vistas for research in the mechanism of AIDS-associated dementia.

2/7/4 (Item 4 from file: 55)
DIALOG(R)File 55:Biosis Preiviews(R)

09668131 BIOSIS NO.: 199598123049
Immunopathogenic role of T-cell subsets in Borna disease virus-induced progressive **encephalitis**.

AUTHOR: Planz Oliver; Bilzer Thomas; Stitz Lothar(a)
AUTHOR ADDRESS: (a)Inst. Virol., Justus-Liebig-Univ., Frankfurter Str. 107, D-35392 Giessen, Germany

JOURNAL: Journal of Virology 69 (2):p896-903 1995
ISSN: 0022-538X
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: Borna disease is an immunopathological virus-induced encephalopathy comprising severe inflammation and degenerative brain cell lesions which results in organ atrophy and chronic debility in rats. CD4+ and CD8+ T cells have been reported to be involved in the development of this disease of the central nervous system. A virus-specific homogeneous T-cell line, established in vitro after immunization of rats with the recombinant 24-kDa virus-specific protein, showed antigen-specific proliferation in the presence of the 24-kDa but not the 38-kDa Borna disease virus-specific protein, another major virus-specific antigen. This T-cell line, P205, was found to exhibit characteristics of a T-helper cell: CD4+ CD8- IL-2- IL-4- IFN-gamma+ IL-6+ IL-10+. Furthermore, this T-cell line expressed the alpha/beta T-cell receptor and the alpha-4 integrin (**VLA-4**). Adoptive transfer of this helper cell resulted in an increase of antibody titers and two different types of disease in virus-infected rats after cyclophosphamide-induced immunosuppression. (i) Rats receiving T cells between 10 and 18 days after treatment with cyclophosphamide showed an acute lymphoproliferative disease in the gut and lungs within 9 days after adoptive transfer and died. (ii) Passive transfer within the first 5 days after immunosuppressive treatment resulted in typical Borna disease associated with neurological symptoms such as ataxia and paresis starting 14 to 16 days after transfer. Immunohistological analysis of the brains of rats with Borna disease uniformly revealed the presence of CD8+ T cells in encephalitic lesions in addition to CD4+ cells that were found in the brains of recipients of the virus-specific CD4+ T-cell line, irrespective of whether neurological symptoms developed or not. However, recipient rats treated with antibodies against CD8+ T cells developed neither **encephalitis** nor disease. Therefore, CD4+ T cells appear to accumulate in the brain and cause perivascular inflammatory lesions which alone obviously do not cause disease. In contrast, the presence of CD8+ cells apparently directly correlates with the development of neurological symptoms.

2/7/5 (Item 5 from file: 55)
DIALOG(R)File 55:Biosis Preiviews(R)

09492703 BIOSIS NO.: 199497501073
Differential expression of ICAM-1, VCAM-1 and their ligands LFA-1, Mac-1, CD43, **VLA-4**, and MHC class II antigens in murine toxoplasma **encephalitis**: A light microscopic and ultrastructural immunohistochemical study.

AUTHOR: Deckert-Schlueter M(a); Schlueter D; Hof H; Wiestler O D; Lassmann L
AUTHOR ADDRESS: (a)Inst. Neuropathologie, Universitaetskliniken Bonn, Sigmund-Freud-Strsse 25, D-53127 Bonn, Germany

JOURNAL: Journal of Neuropathology & Experimental Neurology 53 (5):p 457-468 1994
ISSN: 0022-3069
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: Light microscopic and ultrastructural immunohistochemistry of cell adhesion molecules (CAMs) and major histocompatibility class II antigens (Ia) expression in experimental murine Toxoplasma **encephalitis** (TE) revealed a prominent upregulation of the intercellular cell adhesion molecule-1 (ICAM-1) and of Ia on cerebral endothelia, microglia, ependyma, and choroid plexus epithelium during acute and chronic TE. Microglia also expressed Mac-1 and leukocyte function-associated antigen-1 (LFA-1), which are both ligands of ICAM-1, as well as CD45. The prominent simultaneous expression of a multitude of these molecules on microglia is indicative of a central immunologic function of this cell type in TE. Additionally, occasional astrocytic processes slightly expressed Ia in full-blown TE. The vascular cell adhesion molecule-1 (VCAM-1) was restricted to endothelia of cerebral blood vessels, which frequently showed perivascular cuffing of inflammatory cells, ependyma, and choroid plexus epithelium. Upregulation of Ia, CAMs and their ligands correlated with disease activity. Immunohistochemical analysis of the functional state of infiltrating T cells showed a preferential recruitment of CD44+ memory and activated interleukin-2R+ T cells in TE.

2/7/6 (Item 6 from file: 55)
DIALOG(R)File 55:Biosis Preiviews(R)

08972947 BIOSIS NO.: 199396124448
A model of human immunodeficiency virus **encephalitis** in SCID mice.

AUTHOR: Tyor William R(a); Power Christopher; Gendelman Howard E; Markham Richard B
AUTHOR ADDRESS: (a)Dep. Neurol., Med. Univ. South Carolina, 171 Ashley Ave., Charleston, SC 29425, USA

JOURNAL: Proceedings of the National Academy of Sciences of the United States of America 90 (18):p8658-8662 1993
ISSN: 0027-8424
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: Human immunodeficiency virus (HIV)-associated dementia complex is a common and devastating manifestation of the late phases of HIV infection. The pathogenesis of dementia complex is poorly understood and effective treatments have not been developed, in part because of the lack of an appropriate animal model. Mice with severe combined immunodeficiency (scid mice), which accept xenografts without rejection, were intracerebrally inoculated with human peripheral blood mononuclear cells and HIV. One to 4 weeks after inoculation, the brains of these mice contained human macrophages (some of which were HIV p24 antigen positive), occasional multinucleated cells, and striking gliosis by immunocytochemical staining. Human macrophages also were frequently positive for tumor necrosis factor type a and occasionally for interleukin 1 and **VLA-4**. Cultures of these brains for HIV

were positive. Generally, human macrophages were not present in the brains of control mice, nor was significant gliosis, and HIV was not recovered from mice that received HIV only intracerebrally. Pathologically, this model of HIV **encephalitis** in scid mice resembles HIV **encephalitis** in humans and the data suggest that the activation of macrophages by infection with HIV results in their accumulation and persistence in brain and in the development of gliosis. This model of HIV **encephalitis** should provide insights into the pathogenesis and treatment of this disorder.

2/7/7 (Item 1 from file: 72)
DIALOG(R)File 72:EMBASE

07607385 EMBASE No: 1999008347
Prevention of experimental allergic encephalomyelitis by an antibody to CD45RB
Schiffenbauer J.; Butfiloski E.; Hanley G.; Sobel E.S.; Streit W.J.; Lazarovits A.
J. Schiffenbauer, Department of Medicine, Univ. of Florida College of Medicine, Gainesville, FL 32610 United States
Cellular Immunology (CELL. IMMUNOL.) (United States) 15 DEC 1998, 190/2 (173-182)

CODEN: CLIMB ISSN: 0008-8749
DOCUMENT TYPE: Journal; Article
LANGUAGE: ENGLISH SUMMARY LANGUAGE: ENGLISH
NUMBER OF REFERENCES: 32

CD45 is involved in the regulation of lymphocyte activation, and it has been demonstrated that ligation of CD45 induces apoptosis of T and B lymphocytes. Recently anti-CD45RB antibody therapy was shown to block acute allograft rejection in a mouse model of transplantation. Therefore, we wanted to examine the effects of anti-CD45RB antibody treatment on the course of an autoimmune disorder, experimental allergic encephalomyelitis (EAE), a Th1- mediated process. Mice immunized with myelin basic protein and treated with anti-CD45RB antibody did not develop EAE. Histologically, there was no evidence of lymphocytic infiltrates in the central nervous system. T cell proliferation and TNF-alpha production were significantly decreased in anti- CD45RB-treated mice. Furthermore, there was a significant reduction in the production of other Th1 cytokines including interferon-gamma and IL2, but not IL-4 or IL-6. However, levels of a number of adhesion markers or markers of activation such as **VLA-4** and LFA-1 on T cells were no different in treated versus control animals. Thus, anti-CD45RB can prevent EAE and appears to do so by altering T cell proliferation and cytokine production.

2/7/8 (Item 2 from file: 72)
DIALOG(R)File 72:EMBASE

07589902 EMBASE No: 1999073330
Disproportionate recruitment of CD8sup + T cells into the central nervous system by professional antigen-presenting cells
Carson M.J.; Reilly C.R.; Sutcliffe J.G.; Lo D.
Dr. J.G. Sutcliffe, Department of Molecular Biology, Scripps Research Institute, San Diego, CA 92037 United States
AUTHOR EMAIL: gregor@scripps.edu
American Journal of Pathology (AM. J. PATHOL.) (United States) 1999, 154/2 (481-494)

CODEN: AJPAA ISSN: 0002-9440
DOCUMENT TYPE: Journal; Article

LANGUAGE: ENGLISH SUMMARY LANGUAGE: ENGLISH
NUMBER OF REFERENCES: 44

Inappropriate immune responses, thought to exacerbate or even to initiate several types of central nervous system (CNS) neuropathology, could arise from failures by either the CNS or the immune system. The extent that the inappropriate appearance of antigen-presenting cell (APC) function contributes to CNS inflammation and pathology is still under debate. Therefore, we characterized the response initiated when professional APCs (dendritic cells) presenting non-CNS antigens were injected into the CNS. These dendritic cells expressed numerous T-cell chemokines, but only in the presence of antigen did leukocytes accumulate in the ventricles, meninges, subarachnoid spaces, and injection site. Within the CNS parenchyma, the injected dendritic cells migrated preferentially into the white matter tracts, yet only a small percentage of the recruited leukocytes entered the CNS parenchyma, and then only in the white matter tracts. Although T-cell recruitment was antigen specific and thus mediated by CD4sup + T cells in the models used here, CD8sup + T cells accumulated in numbers equal to or greater than that of CD4sup + T cells. Few of the recruited T cells expressed activation markers (CD25 and **VLA-4**), and those that did were primarily in the meninges, injection site, ventricles, and perivascular spaces but not in the parenchyma. These results indicate that 1) the CNS modulates the cellular composition and activation states of responding T-cell populations and that 2) myelin-restricted inflammation need not be initiated by a myelin-specific antigen.

2/7/9 (Item 3 from file: 72)
DIALOG(R)File 72:EMBASE

05774557 EMBASE No: 1994174195
Lymphocyte adhesion to brain capillary endothelial cells in vitro
De Vries H.E.; Moor A.C.E.; Blom-Roosemalen M.C.M.; De Boer A.G.; Breimer D.D.; Van Berkel T.J.C.; Kuiper J.
Division of Pharmacology, Amsterdam Center Drug Research, University of Leiden, P.O. Box 9503,2300 RA Leiden Netherlands
Journal of Neuroimmunology (J. NEUROIMMUNOL.) (Netherlands) 1994, 52/1 (1-8)

CODEN: JNRID ISSN: 0165-5728
DOCUMENT TYPE: Journal; Article
LANGUAGE: ENGLISH SUMMARY LANGUAGE: ENGLISH

The presence and upregulation of adhesion molecules on bovine brain endothelial cells (BBEC) were investigated. Monolayers of BBEC were incubated with lipopolysaccharide (LPS), interleukin-1beta (rhIL-beta), and interleukin-6 (rhIL-6) to simulate in vitro an inflammatory site in the cerebral capillaries. Adhesion of lymphocytes to BBEC increased 4.1-fold after stimulation of the endothelial cells for 4 h with 5 or 10 ng/ml LPS. Lymphocyte adhesion increased after incubation of the BBEC for 4 h with IL-1 and was increased 3.7-fold using 100 ng/ml IL-1 BBEC pre-incubated with IL-6 for 4 h also showed an increase in adhesion of lymphocytes, and cells pretreated with 100 ng/ml IL-6 showed a 3-fold increase in lymphocyte adherence. Specific monoclonal antibodies directed against CD11a, CD18, and **VLA-4** were able to block adherence of lymphocytes to stimulated BBEC. These results indicate that the in vitro activation of BBEC may serve as a model for the study of inflammation of the blood-brain barrier.

2/7/10 (Item 4 from file: 72)
DIALOG(R)File 72:EMBASE

05751151 EMBASE No: 1994154994

Monocyte adhesion to endothelium in Simian immunodeficiency virus-induced AIDS **encephalitis** is mediated by vascular cell adhesion molecule-1/alpha4beta1 integrin interactions

Sasseville V.G.; Newman W.; Brodie S.J.; Hesterberg P.; Pauley D.; Ringler D.J.

New England Reg. Primate Res. Center, Harvard Medical School, P.O. Box 9102,Southborough, MA 01772-9102 United States

American Journal of Pathology (AM. J. PATHOL.) (United States) 1994, 144/1 (27-40)

CODEN: AJPAA ISSN: 0002-9440
DOCUMENT TYPE: Journal; Article
LANGUAGE: ENGLISH SUMMARY LANGUAGE: ENGLISH

Because the mechanisms associated with recruitment of monocytes to brain in AIDS **encephalitis** are unknown, we used tissues from rhesus monkeys infected with simian immunodeficiency virus (SIV) to examine the relative contributions of various adhesion pathways in mediating monocyte adhesion to endothelium from encephalitic brain. Using a modified Stamper and Woodruff tissue adhesion assay, we found that the human monocytic cell lines, THP-1 and U937, and the B cell line, Ramos, preferentially bound to brain vessels from monkeys with AIDS **encephalitis**. Using a combined tissue adhesion/immunohistochemistry approach, these cells only bound to vessels expressing vascular cell adhesion molecule-1 (VCAM-1). Furthermore, pretreatment of tissues with antibodies to VCAM-1 or cell lines with antibodies to **VLA-4** (CD49d) inhibited adhesion by more than 70%. Intercellular adhesion molecule-1 (ICAM-1)/beta2 integrin interactions were not significant in mediating cell adhesion to the vasculature in encephalitic simian brain using a cell line (JY) capable of binding rhesus monkey ICAM-1. In addition, selectin-mediated interactions did not significantly contribute to cell binding to encephalitic brain as there was no immunohistochemical expression of E-selectin and P-selectin in either normal or encephalitic brain, nor was there a demonstrable adhesive effect from L-selectin using L- selectin-transfected 300.19 cells on simian encephalitic brain. These results demonstrate that using the tissue adhesion assay, THP-1, U937, and Ramos cells bind to vessels in brain from animals with AIDS **encephalitis** using VCAM-1/alpha4beta1 integrin interactions and suggest that VCAM-1 and **VLA-4** may be integral for monocyte recruitment to the central nervous system during the development of AIDS **encephalitis**.

2/7/11 (Item 1 from file: 154)
DIALOG(R)File 154:MEDLINE(R)

09274836 97389373

Humanization of a mouse antibody against human alpha-4 integrin: a potential therapeutic for the treatment of multiple sclerosis.

Leger OJ; Yednock TA; Tanner L; Horner HC; Hines DK; Keen S; Saldanha J; Jones ST; Fritz LC; Bendig MM

MRC Collaborative Centre, London, UK.

Hum Antibodies (UNITED STATES) 1997, 8 (1) p3-16, ISSN 1093-2607 Journal Code: CU3

Languages: ENGLISH

Document type: JOURNAL ARTICLE

alpha 4 beta 1 integrin (**VLA-4**) is crucial for the adhesion of leukocytes to human vascular cell adhesion molecule-1 (VCAM-1) on inflamed endothelium. This cell adhesion event is the first step in leukocyte extravasation across the blood-brain barrier in inflammatory diseases of the central nervous system (CNS) such as experimental autoimmune encephalomyelitis (EAE). Prevention of leukocyte infiltration by antibodies against the alpha 4 integrin, which block the alpha 4 beta 1 integrin/VCAM-1 interaction, have been shown to suppress clinical and pathological features of EAE. In this study, two mouse monoclonal

antibodies (MAb) directed against human alpha 4 integrin were analyzed in vitro for their ability to block the interaction of leukocytes with VCAM-1 under different assay conditions. The best blocking MAb, AN100226m, was humanized by complementarily-determining region grafting, associated with human C regions and expressed. We found that modification of two structural determinants (H27 and H29) for the heavy chain CDR1 loop in one hand, and modification of framework amino acid H38, H40 and H44 in the other hand, had no effect on antigen binding. In contrast, modification of a structural determinant (H71) for the heavy chain CDR2 loop resulted in loss of binding. The humanized antibody. AN100226, was equivalent to the murine antibody. AN100226m, in binding to alpha 4 beta 1 integrin and in blocking cell adhesion. More importantly, AN100226 was as effective as AN100226m in the reversal of active EAE in guinea pigs and thus may be useful in the treatment of autoimmune diseases such as multiple sclerosis. AN100226 is currently in phase II clinical trials in the UK for the treatment of multiple sclerosis exacerbations.

2/7/12 (Item 2 from file: 154)
DIALOG(R)File 154:MEDLINE(R)

08465562 96043309
[HIV and dementia: neuropathology]
Demence et VIH: neuropathologie.
Seilhean D; Duyckaerts C; Hauw JJ
Laboratoire de Neuropathologie R. Escourolle, Hopital de la Salpetriere, Paris.
J Neuroradiol (FRANCE) Sep 1995, 22(3)p161-2, ISSN 0150-9861
Journal Code: JD2
Languages: FRENCH Summary Languages: ENGLISH
Document type: JOURNAL ARTICLE English Abstract
Cognitive disorders associated with HIV infection may be due to focal lesions (lymphoma, toxoplasmosis, progressive multifocal leukoencephalitis, etc.), metabolic encephalopathy (e.g. hepatic insufficiency) or psychiatric disorders (depression). In the absence of such causes a "cognitive and motor syndrome associated with HIV infection" has been defined on clinical criteria (Working group of the American Academy of Neurology, 1991). This syndrome is not consistently associated with any specific lesion. Neither the multifocal **encephalitis** of HIV or CMV infection nor the diffuse leukoencephalopathy associated with HIV are the only causes. The existence of a neocortical neuronal loss has been suggested by several retrospective studies, but our prospective study has not shown cortical or subcortical atrophy. Measurement of neuronal density in Brodmann's areas 4,9 and 40 has not revealed a significant loss either global, by layer, or by column. The only constant lesion was gliosis of the cortex and white matter. Neuronal loss, therefore, is not indispensable to the occurrence of cognitive disorders in AIDS. The mechanism of dementia might be: dysfunction of cortical neurons (dendritic abnormalities, virus/neurotransmitter competition); subcortical dysfunction, as suggested by the high density of microglial nodules in that region; white matter lesions which could be due to abnormalities in the blood-brain barrier. The expression of cell adhesion molecules (VCAM-1, **VLA-4** , ICAM-1 and LFA-1) by endothelial cerebral cells is not significantly different in AIDS patients, demented or not, and in patients with multiple sclerosis. In contrast, the expression of VCAM-1 by astrocytes is significantly increased in demented AIDS patients compared with non demented ones.(ABSTRACT TRUNCATED AT 250 WORDS)

2/7/13 (Item 1 from file: 399)
DIALOG(R)File 399:CA SEARCH(R)

130182768 CA: 130(14)182768q PATENT

Preparation of N-sulfonyl O-carbamoyltyrosine dipeptide derivatives and analogs as inhibitors of leukocyte adhesion mediated by VLA-4

INVENTOR(AUTHOR): Thorsett, Eugene D.; Semko, Christopher M.; Sarantakis, Dimitrios; Pleiss, Michael A.; Kreft, Anthony; Konradi, Andrei W.; Grant, Francine S.; Dressen, Darren B.; Ashwell, Susan; Baudy, Reinhardt Bernhard; Lombardo, Louis John

LOCATION: USA

ASSIGNEE: Athena Neurosciences, Inc.; American Home Products Corporation

PATENT: PCT International ; WO 9906390 A1 DATE: 19990211

APPLICATION: WO 98US15324 (19980731) *US 904424 (19970731) *US 54453 (19970801)

PAGES: 386 pp. CODEN: PIXXD2 LANGUAGE: English CLASS: C07D-311/18A; C07D-207/48B; C07D-277/56B; C07D-279/12B; C07D-277/06B; C07D-403/12B; A61K-031/18B; A61K-031/415B; A61K-031/425B; A61K-031/54B; A61K-031/495B

DESIGNATED COUNTRIES: AL; AM; AT; AU; AZ; BA; BB; BG; BR; BY; CA; CH; CN; CU; CZ; DE; DK; EE; ES; FI; GB; GE; GH; GM; HR; HU; ID; IL; IS; JP; KE; KG; KP; KR; KZ; LC; LK; LR; LS; LT; LU; LV; MD; MG; MK; MN; MW; MX; NO; NZ; PL; PT; RO; RU; SD; SE; SG; SI; SK; SL; TJ; TM; TR; TT; UA; UG; US; US; UZ; VN; YU; ZW; AM; AZ; BY; KG; KZ; MD; RU; TJ; TM DESIGNATED REGIONAL: GH; GM; KE ; LS; MW; SD; SZ; UG; ZW; AT; BE; CH; CY; DE; DK; ES; FI; FR; GB; GR; IE; IT; LU; MC; NL; PT; SE; BF; BJ; CF; CG; CI; CM; GA; GN; GW; ML; MR; NE; SN; TD; TG

SECTION:

CA234003 Amino Acids, Peptides, and Proteins
CA201XXX Pharmacology
CA215XXX Immunochemistry
CA263XXX Pharmaceuticals

IDENTIFIERS: sulfonyl carbamoyltyrosine dipeptide deriv prepn integrin VLA4 binding inhibitor, leukocyte adhesion inhibitor integrin mediated sulfonyl dipeptide prepn

DESCRIPTORS:

Acute lung injury...
leukocyte-mediated; prepn. of N-sulfonyl O-carbamoyltyrosine dipeptide derivs. and analogs as inhibitors of leukocyte adhesion mediated by VLA-4

AIDS dementia... Antiasthmatics... Antiatherosclerotics... Antidiabetic agents... Antirheumatic drugs... Anti-Alzheimer's drugs... Anti-multiple sclerosis agents... Atopic dermatitis...,Encephalitis... Inflammatory bowel diseases... Integrin .alpha.4.beta.1... Leukocyte adhesion... Meningitis... Metastasis inhibitors... Myocardial ischemia... Nephritis... Psoriasis... Stroke... Transplant(organ)...
prepn. of N-sulfonyl O-carbamoyltyrosine dipeptide derivs. and analogs as inhibitors of leukocyte adhesion mediated by VLA-4

Ocular inflammation... Retina...
retinitis; prepn. of N-sulfonyl O-carbamoyltyrosine dipeptide derivs. and analogs as inhibitors of leukocyte adhesion mediated by VLA-4

CAS REGISTRY NUMBERS:

79-44-7 90-05-1 103-76-4 109-01-3 123-90-0 616-34-2 622-40-2
1126-09-6 1192-63-8 2038-03-1 4606-65-9 5382-16-1 13360-57-1
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220551-44-0P 220551-45-1P 220551-46-2P 220551-47-3P 220551-48-4P
220558-29-2P 220558-30-5P 220558-31-6P prepn. of N-sulfonyl O-carbamoyltyrosine dipeptide derivs. and analogs as inhibitors of leukocyte adhesion mediated by VLA-4

103-71-9 111-42-2 reactions, prepn. of N-sulfonyl O-carbamoyltyrosine dipeptide derivs. and analogs as inhibitors of leukocyte adhesion

mediated by VLA-4

2/7/14 (Item 2 from file: 399)
DIALOG(R)File 399:CA SEARCH(R)

130168662 CA: 130(13)168662u PATENT
Preparation of N-sulfonylproline dipeptide derivatives and analogs as inhibitors of leukocyte adhesion mediated by VLA-4
INVENTOR(AUTHOR): Thorsett, Eugene D.; Semko, Christopher M.; Pleiss, Michael A.; Kreft, Anthony; Konradi, Andrei W.; Grant, Francine S.; Baudy, Reinhardt Bernhard; Sarantakis, Dimitrios
LOCATION: USA
ASSIGNEE: Athena Neurosciences, Inc.; American Home Products Corporation
PATENT: PCT International ; WO 9906437 A1 DATE: 19990211
APPLICATION: WO 98US16070 (19980731) *US 904423 (19970731)
PAGES: 294 pp. CODEN: PIXXD2 LANGUAGE: English CLASS: C07K-005/078A; A61K-038/05B DESIGNATED COUNTRIES: AL; AM; AT; AU; AZ; BA; BB; BG; BR; BY; CA; CH; CN; CU; CZ; DE; DK; EE; ES; FI; GB; GE; GH; GM; HR; HU; ID; IL; IS; JP; KE; KG; KP; KR; KZ; LC; LK; LR; LS; LT; LU; LV; MD; MG; MK; MN; MW; MX; NO; NZ; PL; PT; RO; RU; SD; SE; SG; SI; SK; SL; TJ; TM; TR; TT; UA; UG; US; UZ; VN; YU; ZW; AM; AZ; BY; KG; KZ; MD; RU; TJ; TM DESIGNATED REGIONAL: GH ; GM; KE; LS; MW; SD; SZ; UG; ZW; AT; BE; CH; CY; DE; DK; ES; FI; FR; GB; GR; IE; IT; LU; MC; NL; PT; SE; BF; BJ; CF; CG; CI; CM; GA; GN; GW; ML; MR; NE; SN; TD; TG
SECTION:
CA234003 Amino Acids, Peptides, and Proteins
CA201XXX Pharmacology
CA215XXX Immunochemistry
CA263XXX Pharmaceuticals
IDENTIFIERS: sulfonylproline dipeptide deriv prepn integrin VLA4 binding inhibitor, leukocyte adhesion inhibitor integrin mediated sulfonylproline dipeptide prepn
DESCRIPTORS:
Acute lung injury...
leukocyte-mediated; prepn. of N-sulfonylproline dipeptide derivs. and analogs as inhibitors of leukocyte adhesion mediated by VLA-4
AIDS dementia... Antiasthmatics... Antiatherosclerotics... Antidiabetic agents... Antirheumatic drugs... Anti-Alzheimer's drugs... Anti-multiple sclerosis agents... Atopic dermatitis... Dipeptides... Encephalitis... Inflammatory bowel diseases... Integrin .alpha.4.beta.1... Leukocyte adhesion... Meningitis... Metastasis inhibitors... Myocardial ischemia... Nephritis... Psoriasis... Stroke... Transplant(organ)...
prepn. of N-sulfonylproline dipeptide derivs. and analogs as inhibitors of leukocyte adhesion mediated by VLA-4
Ocular inflammation... Retina...
retinitis; prepn. of N-sulfonylproline dipeptide derivs. and analogs as inhibitors of leukocyte adhesion mediated by VLA-4
CAS REGISTRY NUMBERS:
55-43-6 88-65-3 108-01-0 110-62-3 110-78-1 500-22-1 585-71-7
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220365-31-1P prepn. of N-sulfonylproline dipeptide derivs. and analogs as inhibitors of leukocyte adhesion mediated by VLA-4
100-52-7 104-88-1 reactions, prepn. of N-sulfonylproline dipeptide derivs. and analogs as inhibitors of leukocyte adhesion mediated by VLA-4

2/7/15 (Item 3 from file: 399)
DIALOG(R)File 399:CA SEARCH(R)

130168661 CA: 130(13)168661t PATENT
Preparation of N-sulfonyl phenylalanine dipeptide derivatives and analogs as inhibitors of leukocyte adhesion mediated by VLA-4
INVENTOR(AUTHOR): Thorsett, Eugene D.; Semko, Christopher M.; Sarantakis, Dimitrios; Pleiss, Michael A.; Lombardo, Louis John; Kreft, Anthony; Konradi, Andrei W.; Grant, Francine S.; Dressen, Darren B.; Dappen, Michael S.; Baudy, Reinhardt Bernhard; Ashwell, Susan
LOCATION: USA
ASSIGNEE: Athena Neurosciences, Inc.; American Home Products Corporation
PATENT: PCT International ; WO 9906431 A1 DATE: 19990211
APPLICATION: WO 98US15313 (19980730) *US 920394 (19970731)
PAGES: 254 pp. CODEN: PIXXD2 LANGUAGE: English CLASS: C07K-005/062A; C07K-005/065B; C07K-005/078B; A61K-038/05B DESIGNATED COUNTRIES: AL; AM; AT; AU; AZ; BA; BB; BG; BR; BY; CA; CH; CN; CU; CZ; DE; DK; EE; ES; FI; GB; GE; GH; GM; HR; HU; ID; IL; IS; JP; KE; KG; KP; KR; KZ; LC; LK; LR; LS; LT; LU; LV; MD; MG; MK; MN; MW; MX; NO; NZ; PL; PT; RO; RU; SD; SE; SG; SI; SK; SL; TJ; TM; TR; TT; UA; UG; US; UZ; VN; YU; ZW; AM; AZ; BY; KG; KZ; MD; RU; TJ; TM DESIGNATED REGIONAL: GH; GM; KE; LS; MW; SD; SZ; UG; ZW; AT; BE; CH ; CY; DE; DK; ES; FI; FR; GB; GR; IE; IT; LU; MC; NL; PT; SE; BF; BJ; CF; CG; CI; CM; GA; GN; GW; ML; MR; NE; SN; TD; TG
SECTION:
CA234003 Amino Acids, Peptides, and Proteins
CA201XXX Pharmacology
CA215XXX Immunochemistry
CA263XXX Pharmaceuticals
IDENTIFIERS: sulfonyl phenylalanine dipeptide deriv prepn integrin VLA4 binding inhibitor, leukocyte adhesion inhibitor integrin mediated sulfonyl dipeptide prepn
DESCRIPTORS:
Acute lung injury...
leukocyte-mediated; prepn. of N-sulfonyl phenylalanine dipeptide derivs. and analogs as inhibitors of leukocyte adhesion mediated by VLA-4
AIDS dementia... Antiasthmatics... Antiatherosclerotics... Antidiabetic

agents... Antirheumatic drugs... Anti-Alzheimer's drugs... Anti-multiple sclerosis agents... Atopic dermatitis... Encephalitis... Inflammatory bowel diseases... Integrin .alpha.4.beta.1... Leukocyte adhesion... Meningitis... Metastasis inhibitors... Myocardial ischemia... Nephritis... Psoriasis... Stroke... Transplant(organ)...
prepn. of N-sulfonyl phenylalanine dipeptide derivs. and analogs as inhibitors of leukocyte adhesion mediated by VLA-4
Ocular inflammation... Retina...
retinitis; prepn. of N-sulfonyl phenylalanine dipeptide derivs. and analogs as inhibitors of leukocyte adhesion mediated by VLA-4
CAS REGISTRY NUMBERS:
79-07-2 92-49-9 96-79-7 98-80-6 100-10-7 104-16-5 104-77-8 108-01-0
698-92-0 869-24-9 930-36-9 2205-31-4 2532-17-4 2564-06-9
2882-19-1 3040-44-6 3161-52-2 3179-63-3 3240-94-6 3326-32-7
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prepn. of N-sulfonyl phenylalanine dipeptide derivs. and analogs as inhibitors of leukocyte adhesion mediated by VLA-4
108-30-5 reactions, prepn. of N-sulfonyl phenylalanine dipeptide derivs. and analogs as inhibitors of leukocyte adhesion mediated by VLA-4

2/7/16 (Item 4 from file: 399)
DIALOG(R)File 399:CA SEARCH(R)

130153985 CA: 130(12)153985c PATENT
Preparation of N-sulfonylprolylphenylalanine derivatives and analogs as inhibitors of leukocyte adhesion mediated by VLA-4
INVENTOR(AUTHOR): Thorsett, Eugene D.; Semko, Christopher M.; Pleiss, Michael A.; Lombardo, Louis John; Konradi, Andrei W.; Grant, Francine S.; Dressen, Darren B.; Dappen, Michael S.
LOCATION: USA

ASSIGNEE: Athena Neurosciences, Inc.; American Home Products Corporation
PATENT: PCT International ; WO 9906436 A1 DATE: 19990211
APPLICATION: WO 98US15327 (19980731) *US 903585 (19970731)
PAGES: 172 pp. CODEN: PIXXD2 LANGUAGE: English CLASS: C07K-005/078A; C07D-207/16B; A61K-038/05B; A61K-031/40B DESIGNATED COUNTRIES: AL; AM; AT; AU; AZ; BA; BB; BG; BR; BY; CA; CH; CN; CU; CZ; DE; DK; EE; ES; FI; GB; GE; GH; GM; HR; HU; ID; IL; IS; JP; KE; KG; KP; KR; KZ; LC; LK; LR; LS; LT; LU; LV; MD; MG; MK; MN; MW; MX; NO; NZ; PL; PT; RO; RU; SD; SE; SG; SI; SK; SL; TJ; TM; TR; TT; UA; UG; US; UZ; VN; YU; ZW; AM; AZ; BY; KG; KZ; MD; RU; TJ; TM DESIGNATED REGIONAL: GH; GM; KE; LS; MW; SD; SZ; UG; ZW; AT; BE; CH; CY ; DE; DK; ES; FI; FR; GB; GR; IE; IT; LU; MC; NL; PT; SE; BF; BJ; CF; CG; CI; CM; GA; GN; GW; ML; MR; NE; SN; TD; TG
SECTION:
CA234003 Amino Acids, Peptides, and Proteins
CA201XXX Pharmacology
CA215XXX Immunochemistry
CA263XXX Pharmaceuticals
IDENTIFIERS: sulfonylprolylphenylalanine dipeptide deriv prepn integrin VLA4 binding inhibitor, leukocyte adhesion inhibitor integrin mediated sulfonylprolylphenylalanine deriv prepn
DESCRIPTORS:
Acute lung injury...
leukocyte-mediated; prepn. of N-sulfonylprolylphenylalanine derivs. and analogs as inhibitors of leukocyte adhesion mediated by VLA-4
AIDS dementia... Antiasthmatics... Antiatherosclerotics... Antidiabetic agents... Antirheumatic drugs... Anti-Alzheimer's drugs... Anti-multiple sclerosis agents... Atopic dermatitis... Encephalitis... Inflammatory bowel diseases... Integrin .alpha.4.beta.1... Leukocyte adhesion... Meningitis... Metastasis inhibitors... Myocardial ischemia... Nephritis... Psoriasis... Stroke... Transplant(organ)...
prepn. of N-sulfonylprolylphenylalanine derivs. and analogs as inhibitors of leukocyte adhesion mediated by VLA-4
Ocular inflammation... Retina...
retinitis; prepn. of N-sulfonylprolylphenylalanine derivs. and analogs as inhibitors of leukocyte adhesion mediated by VLA-4
CAS REGISTRY NUMBERS:
85-46-1 93-11-8 98-31-7 98-60-2 98-68-0 98-74-8 121-60-8 705-21-5 1939-99-7 2133-40-6 2991-42-6 4410-99-5 10147-37-2 15084-51-2 23095-31-0 26638-43-7 49584-26-1 54690-33-4 78746-23-3 217326-48-2P 217450-71-0P 220149-81-5 220149-82-6 220186-85-6P 220186-87-8P 220186-88-9P 220186-89-0P 220186-90-3P 220186-91-4P 220186-92-5P 220186-94-7P 220186-95-8P 220186-96-9P 220186-97-0P 220186-98-1P 220186-99-2P 220187-00-8P 220187-01-9P 220187-02-0P 220187-03-1P 220187-04-2P 220187-05-3P 220187-06-4P 220187-07-5P 220187-08-6P 220187-09-7P 220187-10-0P 220187-11-1P 220187-12-2P 220187-13-3P 220187-14-4P 220187-15-5P 220187-16-6P 220187-17-7P 220187-18-8P 220187-19-9P 220187-20-2P 220187-21-3P 220187-22-4P 220187-23-5P 220187-24-6P 220187-25-7P 220187-26-8P 220187-27-9P 220187-28-0P 220187-29-1P 220187-30-4P 220187-31-5P 220187-32-6P 220187-33-7P 220187-34-8P 220187-35-9P 220187-36-0P 220187-37-1P 220187-38-2P 220187-39-3P 220187-40-6P 220187-41-7P 220187-42-8P 220187-43-9P 220187-44-0P 220187-45-1P 220187-46-2P 220187-47-3P 220187-48-4P 220187-49-5P 220187-50-8P 220187-51-9P 220187-52-0P 220187-53-1P 220187-54-2P 220187-55-3P 220187-56-4P 220187-57-5P 220187-58-6P 220187-59-7P 220187-60-0P 220187-61-1P 220187-62-2P 220187-63-3P 220187-64-4P 220187-65-5P 220187-66-6P 220187-67-7P 220187-68-8P 220187-69-9P 220187-70-2P 220187-71-3P 220187-72-4P 220187-73-5P 220187-74-6P 220187-75-7P 220187-76-8P 220187-77-9P 220187-78-0P 220187-79-1P 220187-80-4P 220187-81-5P 220187-82-6 220187-83-7P 220187-84-8P prepn. of N-sulfonylprolylphenylalanine derivs. and analogs as inhibitors of leukocyte adhesion mediated by VLA-4

2/7/17 (Item 5 from file: 399)

130153984 CA: 130(12)153984b PATENT

Preparation of N-sulfonyl dipeptide derivatives and analogs as inhibitors of leukocyte adhesion mediated by VLA-4

INVENTOR(AUTHOR): Thorsett, Eugene D.; Semko, Christopher M.; Pleiss, Michael A.; Konradi, Andrei W.; Grant, Francine S.; Dressen, Darren B.; Baudy, Reinhardt Bernhard
LOCATION: USA
ASSIGNEE: Athena Neurosciences, Inc.; American Home Products Corporation

PATENT: PCT International ; WO 9906435 A1 DATE: 19990211
APPLICATION: WO 98US15314 (19980730) *US 904415 (19970731)
PAGES: 151 pp. CODEN: PIXXD2 LANGUAGE: English CLASS: C07K-005/078A; C07K-005/062B; C07K-005/065B; A61K-038/05B DESIGNATED COUNTRIES: AL; AM; AT; AU; AZ; BA; BB; BG; BR; BY; CA; CH; CN; CU; CZ; DE; DK; EE; ES; FI; GB; GE; GH; GM; HR; HU; ID; IL; IS; JP; KE; KG; KP; KR; KZ; LC; LK; LR; LS; LT; LU; LV; MD; MG; MK; MN; MW; MX; NO; NZ; PL; PT; RO; RU; SD; SE; SG; SI; SK; SL; TJ; TM; TR; TT; UA; UG; US; UZ; VN; YU; ZW; AM; AZ; BY; KG; KZ; MD; RU; TJ; TM DESIGNATED REGIONAL: GH; GM; KE; LS; MW; SD; SZ; UG; ZW; AT; BE; CH ; CY; DE; DK; ES; FI; FR; GB; GR; IE; IT; LU; MC; NL; PT; SE; BF; BJ; CF; CG; CI; CM; GA; GN; GW; ML; MR; NE; SN; TD; TG

SECTION:
CA234003 Amino Acids, Peptides, and Proteins
CA201XXX Pharmacology
CA215XXX Immunochemistry
CA263XXX Pharmaceuticals

IDENTIFIERS: sulfonyl dipeptide deriv prepn integrin VLA4 binding inhibitor, leukocyte adhesion inhibitor integrin mediated sulfonyl dipeptide deriv prepn

DESCRIPTORS:
Acute lung injury...
leukocyte-mediated; prepn. of N-sulfonyl dipeptide derivs. and analogs as inhibitors of leukocyte adhesion mediated by VLA-4
AIDS dementia... Antiasthmatics... Antiatherosclerotics... Antidiabetic agents... Antirheumatic drugs... Anti-Alzheimer's drugs... Anti-multiple sclerosis agents... Atopic dermatitis... Encephalitis... Inflammatory bowel diseases... Integrin .alpha.4.beta.1... Leukocyte adhesion... Meningitis... Metastasis inhibitors... Myocardial ischemia... Nephritis... Psoriasis... Stroke... Transplant(organ)...
prepn. of N-sulfonyl dipeptide derivs. and analogs as inhibitors of leukocyte adhesion mediated by VLA-4
Ocular inflammation... Retina...
retinitis; prepn. of N-sulfonyl dipeptide derivs. and analogs as inhibitors of leukocyte adhesion mediated by VLA-4

CAS REGISTRY NUMBERS:
14254-57-0 54690-33-4 220149-81-5 220149-82-6 220172-64-5P
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220173-56-8P 220173-57-9P 220173-59-1P 220173-64-8P prepn. of N-sulfonyl dipeptide derivs. and analogs as inhibitors of leukocyte adhesion mediated by VLA-4

2/7/18 (Item 6 from file: 399)

DIALOG(R)File 399:CA SEARCH(R)

130153983 CA: 130(12)153983a PATENT

Preparation of N-sulfonylated aminophenylalanine dipeptide derivatives and analogs as inhibitors of leukocyte adhesion mediated by VLA-4

INVENTOR(AUTHOR): Ashwell, Susan; Grant, Francine S.; Konradi, Andrei W.; Kreft, Anthony; Lombardo, Louis John; Pleiss, Michael A.; Sarantakis, Dimitrios; Semko, Christopher M.; Thorsett, Eugene D.

LOCATION: USA

ASSIGNEE: Athena Neurosciences, Inc.; American Home Products Corporation

PATENT: PCT International ; WO 9906434 A1 DATE: 19990211

APPLICATION: WO 98US15312 (19980730) *US 920353 (19970731)

PAGES: 164 pp. CODEN: PIXXD2 LANGUAGE: English CLASS: C07K-005/078A; A61K-038/05B DESIGNATED COUNTRIES: AL; AM; AT; AU; AZ; BA; BB; BG; BR; BY; CA; CH; CN; CU; CZ; DE; DK; EE; ES; FI; GB; GE; GH; GM; HR; HU; ID; IL; IS; JP; KE; KG; KP; KR; KZ; LC; LK; LR; LS; LT; LU; LV; MD; MG; MK; MN; MW; MX; NO; NZ; PL; PT; RO; RU; SD; SE; SG; SI; SK; SL; TJ; TM; TR; TT; UA; UG; US; UZ; VN; YU; ZW; AM; AZ; BY; KG; KZ; MD; RU; TJ; TM DESIGNATED REGIONAL: GH ; GM; KE; LS; MW; SD; SZ; UG; ZW; AT; BE; CH; CY; DE; DK; ES; FI; FR; GB; GR; IE; IT; LU; MC; NL; PT; SE; BF; BJ; CF; CG; CI; CM; GA; GN; GW; ML; MR; NE; SN; TD; TG

SECTION:
CA234003 Amino Acids, Peptides, and Proteins
CA201XXX Pharmacology
CA215XXX Immunochemistry
CA263XXX Pharmaceuticals

IDENTIFIERS: sulfonyl aminophenylalanine dipeptide deriv prepn integrin VLA4 binding inhibitor, leukocyte adhesion inhibitor integrin mediated sulfonyl aminophenylalanine dipeptide prepn

DESCRIPTORS:
Acute lung injury...
leukocyte-mediated; prepn. of N-sulfonylated aminophenylalanine dipeptide derivs. and analogs as inhibitors of leukocyte adhesion mediated by VLA-4
AIDS dementia... Antiasthmatics... Antiatherosclerotics... Antidiabetic agents... Antirheumatic drugs... Anti-Alzheimer's drugs... Anti-multiple sclerosis agents... Atopic dermatitis... Encephalitis... Inflammatory bowel diseases... Integrin .alpha.4.beta.1... Leukocyte adhesion... Meningitis... Metastasis inhibitors... Myocardial ischemia... Nephritis... Psoriasis... Stroke... Transplant(organ)...
prepn. of N-sulfonylated aminophenylalanine dipeptide derivs. and analogs as inhibitors of leukocyte adhesion mediated by VLA-4
Ocular inflammation... Retina...
retinitis; prepn. of N-sulfonylated aminophenylalanine dipeptide derivs. and analogs as inhibitors of leukocyte adhesion mediated by VLA-4

CAS REGISTRY NUMBERS:
109-01-3 1943-82-4 2257-09-2 2627-27-2 32813-24-4 32813-50-6
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220150-61-8P 220150-62-9P 220202-29-9P 220202-30-2P prepn. of
N-sulfonylated aminophenylalanine dipeptide derivs. and analogs as
inhibitors of leukocyte adhesion mediated by VLA-4

2/7/19 (Item 7 from file: 399)
DIALOG(R)File 399:CA SEARCH(R)

130153982 CA: 130(12)153982z PATENT
Preparation of N-sulfonyl phenylalanine dipeptide derivatives and analogs as inhibitors of leukocyte adhesion mediated by VLA-4
INVENTOR(AUTHOR): Dappen, Michael S.; Dressen, Darren B.; Grant, Francine S.; Pleiss, Michael A.; Robinson, Cynthia Y.; Sarantakis, Dimitrios; Thorsett, Eugene D.
LOCATION: USA
ASSIGNEE: Athena Neurosciences, Inc.; American Home Products Corporation
PATENT: PCT International ; WO 9906433 A1 DATE: 19990211
APPLICATION: WO 98US15952 (19980731) *US 904416 (19970731)
PAGES: 190 pp. CODEN: PIXXD2 LANGUAGE: English CLASS: C07K-005/062A; C07K-005/065B; C07K-005/072B; C07K-005/078B; A61K-038/05B
DESIGNATED COUNTRIES: AL; AM; AT; AU; AZ; BA; BB; BG; BR; BY; CA; CH; CN; CU; CZ; DE; DK; EE; ES; FI; GB; GE; GH; GM; HR; HU; ID; IL; IS; JP; KE; KG; KP; KR; KZ; LC; LK; LR; LS; LT; LU; LV; MD; MG; MK; MN; MW; MX; NO; NZ; PL; PT; RO; RU; SD; SE; SG; SI; SK; SL; TJ; TM; TR; TT; UA; UG; US; UZ; VN; YU; ZW; AM; AZ; BY; KG; KZ; MD; RU; TJ; TM DESIGNATED REGIONAL: GH; GM; KE; LS ; MW; SD; SZ; UG; ZW; AT; BE; CH; CY; DE; DK; ES; FI; FR; GB; GR; IE; IT; LU; MC; NL; PT; SE; BF; BJ; CF; CG; CI; CM; GA; GN; GW; ML; MR; NE; SN; TD; TG
SECTION:
CA234003 Amino Acids, Peptides, and Proteins
CA201XXX Pharmacology
CA215XXX Immunochemistry
CA263XXX Pharmaceuticals
IDENTIFIERS: sulfonyl phenylalanine dipeptide deriv prepn integrin VLA4 binding inhibitor, leukocyte adhesion inhibitor integrin mediated sulfonyl phenylalanine dipeptide prepn
DESCRIPTORS:
Acute lung injury...
leukocyte-mediated; prepn. of N-sulfonyl phenylalanine dipeptide derivs. and analogs as inhibitors of leukocyte adhesion mediated by VLA-4
AIDS dementia... Antiasthmatics... Antiatherosclerotics... Antidiabetic agents... Antirheumatic drugs... Anti-Alzheimer's drugs... Anti-multiple sclerosis agents... Atopic dermatitis... Dipeptides... Encephalitis... Inflammatory bowel diseases... Integrin .alpha.4.beta.1... Leukocyte adhesion... Meningitis... Metastasis inhibitors... Myocardial ischemia... Nephritis... Psoriasis... Stroke... Transplant(organ)...
prepn. of N-sulfonyl phenylalanine dipeptide derivs. and analogs as inhibitors of leukocyte adhesion mediated by VLA-4
Ocular inflammation... Retina...
retinitis; prepn. of N-sulfonyl phenylalanine dipeptide derivs. and analogs as inhibitors of leukocyte adhesion mediated by VLA-4
CAS REGISTRY NUMBERS:
1068-90-2 1822-51-1 2566-30-5 4809-57-8P 6959-48-4 14254-57-0
19525-87-2 26638-43-7 40056-02-8P 53459-50-0 54690-33-4
103733-08-0P 124312-54-5P 208259-58-9P 220149-82-6 220176-98-7
220185-84-2P 220185-85-3P 220185-86-4P 220185-87-5P 220185-88-6P
220185-89-7P 220185-90-0P 220185-91-1P 220185-92-2P 220185-93-3P
220185-94-4P 220185-95-5P 220185-96-6P 220185-97-7P 220185-98-8P

220185-99-9P 220186-00-5P 220186-01-6P 220186-02-7P 220186-03-8P
220186-04-9P 220186-05-0P 220186-06-1P 220186-07-2P 220186-08-3P
220186-09-4P 220186-10-7P 220186-11-8P 220186-12-9P 220186-13-0P
220186-14-1P 220186-15-2P 220186-16-3P 220186-17-4P 220186-18-5P
220186-19-6P 220186-20-9P 220186-21-0P 220186-22-1P 220186-23-2P
220186-24-3P 220186-26-5P 220186-27-6P 220186-28-7P 220186-29-8P
220186-30-1P 220186-31-2P 220186-33-4P 220186-34-5P 220186-35-6P
220186-37-8P 220186-38-9P 220186-39-0 prepn. of N-sulfonyl phenylalanine dipeptide derivs. and analogs as inhibitors of leukocyte adhesion mediated by VLA-4

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FILE 'USPAT' ENTERED AT 12:19:04 ON 13 JUN 1999

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*        U. S.   P A T E N T   T E X T   F I L E                       *
*                                                                       *
*  THE WEEKLY PATENT TEXT AND IMAGE DATA IS CURRENT                     *
*  THROUGH June 8,1999.                                                 *
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=> s (encephalitis or arbovirus or herpes)(P)(vla(w)4 or alpha(w)4)

          1375 ENCEPHALITIS
            87 ARBOVIRUS
          6639 HERPES
           343 VLA
       2397640 4
        272225 ALPHA
       2397640 4
L1           25 (ENCEPHALITIS OR ARBOVIRUS OR HERPES)(P)(VLA(W)4 OR ALPHA(W
)4)

=> d l1 1-25
```

1. 5,879,934, Mar. 9, 1999, Herpes simplex virus strains for gene transfer; Neal A. DeLuca, 435/320.1; 536/23.72 [IMAGE AVAILABLE]

2. 5,876,923, Mar. 2, 1999, Herpes simplex virus ICP4 as an inhibitor of apoptosis; Rosario Leopardi, et al., 435/5; 424/93.1, 93.2; 435/6, 69.2; 514/44 [IMAGE AVAILABLE]

3. 5,874,279, Feb. 23, 1999, Recombinant infectious bovine rhinotracheitis virus; Mark D. Cochran, et al., 435/235.1, 320.1 [IMAGE AVAILABLE]

4. 5,853,733, Dec. 29, 1998, Recombinant herpesvirus of turkeys and uses thereof; Mark D. Cochran, et al., 424/199.1, 229.1, 816; 435/69.1, 69.3, 235.1, 320.1 [IMAGE AVAILABLE]

5. 5,846,707, Dec. 8, 1998, Herpes simplex virus as a vector; Bernard Roizman, 435/5, 6, 69.1, 91.41, 320.1, 465 [IMAGE AVAILABLE]

6. 5,840,299, Nov. 24, 1998, Humanized antibodies against leukocyte adhesion molecule VLA-4; Mary M. Bendig, et al., 424/133.1, 130.1, 141.1, 143.1, 144.1, 153.1, 154.1, 173.1; 435/7.1, 7.2, 7.21, 7.24, 69.6, 320.1; 530/387.3, 388.22, 388.73, 388.75; 536/23.53 [IMAGE AVAILABLE]

7. 5,804,413, Sep. 8, 1998, Herpes simplex virus strains for gene transfer; Neal A. DeLuca, 435/69.1, 235.1, 320.1, 364, 456, 463 [IMAGE AVAILABLE]

8. 5,804,372, Sep. 8, 1998, Method of distinguishing an IBRV-vaccinated bovine from a bovine infected with a wild type virus; Mark D. Cochran, et al., 435/5; 424/229.1; 435/7.1 [IMAGE AVAILABLE]

9. 5,783,195, Jul. 21, 1998, Recombinant infectious bovine rhinotracheitis virus S-IBR-052 and uses thereof; Mark D. Cochran, et al., 424/229.1; 435/235.1, 236 [IMAGE AVAILABLE]

10. 5,747,253, May 5, 1998, Combinatorial oligomer immunoabsorbant screening assay for transcription factors and other biomolecule binding; David J. Ecker, et al., 435/6, 7.1; 536/24.1, 25.3 [IMAGE AVAILABLE]

11. 5,744,362, Apr. 28, 1998, Antisense oligonucleotide modulation of raf gene expression; Brett P. Monia, et al., 435/375; 514/44; 536/24.5 [IMAGE AVAILABLE]

12. 5,733,554, Mar. 31, 1998, Avian herpesvirus-based live recombinant avian vaccine, in particular against Gumboro disease; Jean-Christophe Fran.cedilla.is Audonnet, et al., 424/199.1, 204.1, 229.1; 435/235.1,

320.1 [IMAGE AVAILABLE]

13. 5,714,153, Feb. 3, 1998, Method of inducing antibody production against an infectious agent in a host; Bernard Roizman, 424/231.1, 93.2, 93.6 [IMAGE AVAILABLE]

14. 5,672,344, Sep. 30, 1997, Viral-mediated gene transfer system; William N. Kelley, et al., 424/93.2, 93.6; 435/320.1, 368, 455 [IMAGE AVAILABLE]

15. 5,658,724, Aug. 19, 1997, Herpes simplex virus strains deficient for the essential immediate early genes ICP4 and ICP27 and methods for their production, growth and use; Neal A. DeLuca, 435/5, 235.1, 236, 320.1, 325, 364, 465 [IMAGE AVAILABLE]

16. 5,641,651, Jun. 24, 1997, Synthetic herpes simplex virus promoters; Bernard Roizman, 435/69.1, 320.1, 456; 536/23.1, 24.1 [IMAGE AVAILABLE]

17. 5,599,691, Feb. 4, 1997, Herpes simplex virus as a vector; Bernard Roizman, 435/69.1, 320.1, 463, 465 [IMAGE AVAILABLE]

18. 5,599,676, Feb. 4, 1997, Method for isolating a novel receptor for .alpha.4 integrins; Robert H. Vonderheide, et al., 435/7.2, 69.1, 91.1, 252.3, 252.33, 254.11, 320.1; 530/387.1; 536/23.1 [IMAGE AVAILABLE]

19. 5,599,544, Feb. 4, 1997, Recombinant infectious bovine rhinotracheitis virus; Mark D. Cochran, et al., 424/229.1; 435/235.1 [IMAGE AVAILABLE]

20. 5,593,873, Jan. 14, 1997, Recombinant infectious bovine rhinotracheitis virus; Mark D. Cochran, et al., 435/235.1, 320.1 [IMAGE AVAILABLE]

21. 5,532,124, Jul. 2, 1996, Genetically engineered bacteria to identify and produce medically important agents; Timothy M. Block, et al., 435/5, 6, 23, 34, 68.1, 69.1, 69.2, 184, 244, 252.3, 974 [IMAGE AVAILABLE]

22. 5,478,727, Dec. 26, 1995, Methods and compositions for the preparation and use of a herpes protease; Bernard Roizman, et al., 435/23, 5, 219, 235.1 [IMAGE AVAILABLE]

23. 5,324,664, Jun. 28, 1994, Herpes virus thymidien kinase-encoding DNA; Jack H. Nunberg, et al., 435/320.1, 69.1, 235.1; 530/350; 536/23.1, 23.72, 24.1 [IMAGE AVAILABLE]

24. 5,288,641, Feb. 22, 1994, Herpes Simplex virus as a vector; Bernard Roizman, 435/320.1, 6, 69.1, 476 [IMAGE AVAILABLE]

25. 4,859,587, Aug. 22, 1989, Recombinant herpes simplex viruses, vaccines and methods; Bernard Roizman, 424/199.1, 231.1; 435/235.1, 317.1, 320.1, 455, 465; 536/23.2, 23.72 [IMAGE AVAILABLE]

=> d l1 1-25 date

L1: 1 of 25

TITLE: Herpes simplex virus strains for gene transfer
US PAT NO: 5,879,934 DATE ISSUED: Mar. 9, 1999
[IMAGE AVAILABLE]
APPL-NO: 08/479,024 DATE FILED: Jun. 7, 1995
REL-US-DATA: Continuation-in-part of Ser. No. 342,795, Nov. 21, 1994, which is a continuation of Ser. No. 922,839, Jul. 31, 1992, abandoned.

L1: 2 of 25

TITLE: Herpes simplex virus ICP4 as an inhibitor of apoptosis
US PAT NO: 5,876,923 DATE ISSUED: Mar. 2, 1999
[IMAGE AVAILABLE]
APPL-NO: 08/690,473 DATE FILED: Jul. 26, 1996

L1: 3 of 25

TITLE: Recombinant infectious bovine rhinotracheitis virus
US PAT NO: 5,874,279 DATE ISSUED: Feb. 23, 1999
[IMAGE AVAILABLE]
APPL-NO: 08/185,949 DATE FILED: Nov. 3, 1994
PCT-NO: PCT/US92/06034 PCT-FILED: Jul. 20, 1992
371-DATE: Nov. 3, 1994
102(E)-DATE: Nov. 3, 1994
PCT-PUB-NO: WO93/02104 PCT-PUB-DATE: Feb. 4, 1993
REL-US-DATA: Continuation-in-part of Ser. No. 732,584, Jul. 18, 1991, abandoned.

L1: 4 of 25

TITLE: Recombinant herpesvirus of turkeys and uses thereof
US PAT NO: 5,853,733 DATE ISSUED: Dec. 29, 1998
[IMAGE AVAILABLE]
APPL-NO: 08/663,566 DATE FILED: Jun. 13, 1996
REL-US-DATA: Continuation of Ser. No. 288,065, Aug. 9, 1994, which is a continuation-in-part of Ser. No. 23,610, Feb. 26, 1993.

L1: 5 of 25

TITLE: Herpes simplex virus as a vector
US PAT NO: 5,846,707 DATE ISSUED: Dec. 8, 1998
[IMAGE AVAILABLE]
APPL-NO: 08/791,852 DATE FILED: Jan. 31, 1997
REL-US-DATA: Continuation of Ser. No. 419,831, Apr. 11, 1995, Pat. No. 5,599,691, Feb. 4, 1997, which is a continuation of Ser. No. 195,356, Feb. 10, 1994, abandoned, which is a continuation of Ser. No. 923,015, Jul. 30, 1992, Pat. No. 5,288,641, Feb. 22, 1994, which is a continuation of Ser. No. 455,771, Dec. 28, 1989, abandoned, which is a continuation of Ser. No. 616,930, Jun. 4, 1984, abandoned.

L1: 6 of 25

TITLE: Humanized antibodies against leukocyte adhesion molecule VLA-4
US PAT NO: 5,840,299 DATE ISSUED: Nov. 24, 1998
[IMAGE AVAILABLE]
APPL-NO: 08/561,521 DATE FILED: Nov. 21, 1995
REL-US-DATA: Continuation-in-part of Ser. No. 186,269, Jan. 25, 1994, abandoned.

L1: 7 of 25

TITLE: Herpes simplex virus strains for gene transfer
US PAT NO: 5,804,413 DATE ISSUED: Sep. 8, 1998
[IMAGE AVAILABLE]
APPL-NO: 08/651,419 DATE FILED: May 22, 1996
REL-US-DATA: Continuation-in-part of Ser. No. 479,024, Jun. 7, 1995, which is a continuation-in-part of Ser. No. 342,795, Nov. 21, 1994, Pat. No. 5,658,724, which is a continuation of Ser. No. 922,839, Jul. 31, 1992, abandoned.

L1: 8 of 25

TITLE: Method of distinguishing an IBRV-vaccinated bovine from a bovine infected with a wild type virus
US PAT NO: 5,804,372 DATE ISSUED: Sep. 8, 1998
[IMAGE AVAILABLE]
APPL-NO: 08/674,169 DATE FILED: Jul. 1, 1996

REL-US-DATA: Continuation of Ser. No. 247,475, May 23, 1994, Pat. No. 5,593,873, which is a continuation of Ser. No. 732,584, Jul. 18, 1991, abandoned, which is a continuation-in-part of Ser. No. 696,262, Apr. 30, 1991, abandoned, which is a continuation of Ser. No. 933,107, Nov. 20, 1986, abandoned, and a continuation-in-part of Ser. No. 649,380, Jan. 31, 1991, abandoned, which is a continuation of Ser. No. 78,519, Jul. 27, 1987, abandoned, and a continuation-in-part of Ser. No. 225,032, Jul. 27, 1988, Pat. No. 5,223,424, Ser. No. 823,102, Jan. 27, 1986, Pat. No. 5,068,192, and Ser. No. 192,866, May 11, 1988, Pat. No. 5,047,237.

L1: 9 of 25

TITLE: Recombinant infectious bovine rhinotracheitis virus S-IBR-052 and uses thereof
US PAT NO: 5,783,195 DATE ISSUED: Jul. 21, 1998
[IMAGE AVAILABLE]
APPL-NO: 08/191,866 DATE FILED: Feb. 4, 1994
REL-US-DATA: Continuation-in-part of Ser. No. 732,584, Jul. 18, 1991, abandoned.

L1: 10 of 25

TITLE: Combinatorial oligomer immunoabsorbant screening assay for transcription factors and other biomolecule binding
US PAT NO: 5,747,253 DATE ISSUED: May 5, 1998
[IMAGE AVAILABLE]
APPL-NO: 08/386,141 DATE FILED: Feb. 8, 1995
REL-US-DATA: Continuation-in-part of Ser. No. 357,396, Dec. 16, 1994, which is a continuation-in-part of Ser. No. 196,103, Feb. 22, 1994, which is a continuation-in-part of Ser. No. 749,000, Aug. 23, 1991, abandoned.

L1: 11 of 25

TITLE: Antisense oligonucleotide modulation of raf gene expression
US PAT NO: 5,744,362 DATE ISSUED: Apr. 28, 1998
[IMAGE AVAILABLE]
APPL-NO: 08/463,912 DATE FILED: Jun. 5, 1995
REL-US-DATA: Continuation-in-part of Ser. No. 250,856, May 31, 1994, Pat. No. 5,563,255.

L1: 12 of 25

TITLE: Avian herpesvirus-based live recombinant avian vaccine, in particular against Gumboro disease
US PAT NO: 5,733,554 DATE ISSUED: Mar. 31, 1998
[IMAGE AVAILABLE]
APPL-NO: 08/368,803 DATE FILED: Jan. 5, 1995
FRN-PR. NO: 94 16015 FRN FILED: Dec. 30, 1994
FRN-PR. CO: France

L1: 13 of 25

TITLE: Method of inducing antibody production against an infectious agent in a host
US PAT NO: 5,714,153 DATE ISSUED: Feb. 3, 1998
[IMAGE AVAILABLE]
APPL-NO: 08/681,811 DATE FILED: Jul. 29, 1996
REL-US-DATA: Continuation of Ser. No. 332,467, Oct. 31, 1994, Pat. No. 5,641,651, which is a continuation of Ser. No. 996,961, Dec. 23, 1992, abandoned.

L1: 14 of 25

TITLE: Viral-mediated gene transfer system
US PAT NO: 5,672,344 DATE ISSUED: Sep. 30, 1997
[IMAGE AVAILABLE]

APPL-NO: 08/194,794 DATE FILED: Feb. 10, 1994
REL-US-DATA: Continuation of Ser. No. 737,035, Jul. 29, 1991, abandoned, which is a continuation of Ser. No. 139,597, Dec. 30, 1987, abandoned.

L1: 15 of 25

TITLE: Herpes simplex virus strains deficient for the essential immediate early genes ICP4 and ICP27 and methods for their production, growth and use
US PAT NO: 5,658,724 DATE ISSUED: Aug. 19, 1997
[IMAGE AVAILABLE]
APPL-NO: 08/342,795 DATE FILED: Nov. 21, 1994
REL-US-DATA: Continuation of Ser. No. 922,839, Jul. 31, 1992, abandoned.

L1: 16 of 25

TITLE: Synthetic herpes simplex virus promoters
US PAT NO: 5,641,651 DATE ISSUED: Jun. 24, 1997
[IMAGE AVAILABLE]
APPL-NO: 08/332,467 DATE FILED: Oct. 31, 1994
REL-US-DATA: Continuation of Ser. No. 996,961, Dec. 23, 1992, abandoned.

L1: 17 of 25

TITLE: Herpes simplex virus as a vector
US PAT NO: 5,599,691 DATE ISSUED: Feb. 4, 1997
[IMAGE AVAILABLE]
APPL-NO: 08/419,831 DATE FILED: Apr. 11, 1995
REL-US-DATA: Continuation of Ser. No. 195,356, Feb. 10, 1994, abandoned, which is a continuation of Ser. No. 923,015, Jul. 30, 1992, Pat. No. 5,288,641, Feb. 22, 1994, which is a continuation of Ser. No. 455,771, Dec. 28, 1989, abandoned, which is a continuation of Ser. No. 616,930, Jun. 4, 1984, abandoned.

L1: 18 of 25

TITLE: Method for isolating a novel receptor for .alpha.4 integrins
US PAT NO: 5,599,676 DATE ISSUED: Feb. 4, 1997
[IMAGE AVAILABLE]
APPL-NO: 08/323,199 DATE FILED: Oct. 14, 1994
REL-US-DATA: Continuation of Ser. No. 886,992, May 21, 1992, abandoned.

L1: 19 of 25

TITLE: Recombinant infectious bovine rhinotracheitis virus
US PAT NO: 5,599,544 DATE ISSUED: Feb. 4, 1997
[IMAGE AVAILABLE]
APPL-NO: 08/479,650 DATE FILED: Jun. 7, 1995
REL-US-DATA: Continuation of Ser. No. 247,475, May 23, 1994, which is a continuation of Ser. No. 732,584, Jul. 18, 1991, abandoned, which is a continuation-in-part of Ser. No. 696,262, Apr. 30, 1991, abandoned, which is a continuation of Ser. No. 933,107, Nov. 20, 1986, abandoned, and a continuation-in-part of Ser. No. 649,380, Jan. 31, 1991, abandoned, which is a continuation of Ser. No. 78,519, Jul. 27, 1987, abandoned, and a continuation-in-part of Ser. No. 225,032, Jul. 27, 1988, Pat. No. 5,223,424, Jun. 29, 1993, Ser. No. 823,102, Jan. 27, 1986, Pat. No. 5,068,192, Nov. 26, 1991, and Ser. No. 192,866, May 11, 1988, Pat. No. 5,047,237, Sep. 10, 1991.

L1: 20 of 25

TITLE: Recombinant infectious bovine rhinotracheitis virus
US PAT NO: 5,593,873 DATE ISSUED: Jan. 14, 1997

[IMAGE AVAILABLE]
APPL-NO: 08/247,475 DATE FILED: May 23, 1994
REL-US-DATA: Continuation-in-part of Ser. No. 649,380, Jan. 31, 1991, abandoned, Ser. No. 225,032, Jul. 27, 1988, Pat. No. 5,223,424, Jun. 29, 1993, Ser. No. 823,102, Jan. 27, 1986, Pat. No. 5,068,192, Nov. 26, 1991, and Ser. No. 192,866, May 19, 1988, Pat. No. 5,047,237, Sep. 10, 1991, and a continuation of Ser. No. 732,584, Jul. 19, 1991, abandoned, which is a continuation-in-part of Ser. No. 696,262, Apr. 19, 1991, abandoned, which is a continuation of Ser. No. 933,107, Nov. 19, 1986, abandoned, said Ser. No. 649,380 is a continuation of Ser. No. 78,519, Jul. 27, 1987, abandoned.

L1: 21 of 25

TITLE: Genetically engineered bacteria to identify and produce medically important agents
US PAT NO: 5,532,124 DATE ISSUED: Jul. 2, 1996
[IMAGE AVAILABLE]
APPL-NO: 08/098,313 DATE FILED: Oct. 6, 1993
FRN-PR. NO: PCT/US91/07294 FRN FILED: Oct. 4, 1991
FRN-PR. CO: World Intellectual Property Organization
PCT-NO: PCT/US92/01188 PCT-FILED: Feb. 11, 1992
371-DATE: Oct. 6, 1993
102(E)-DATE: Oct. 6, 1993
PCT-PUB-NO: WO92/13972 PCT-PUB-DATE: Aug. 20, 1992
REL-US-DATA: Continuation-in-part of Ser. No. 654,064, Feb. 11, 1991, abandoned.

L1: 22 of 25

TITLE: Methods and compositions for the preparation and use of a herpes protease
US PAT NO: 5,478,727 DATE ISSUED: Dec. 26, 1995
[IMAGE AVAILABLE]
APPL-NO: 07/832,855 DATE FILED: Feb. 7, 1992
REL-US-DATA: Continuation-in-part of Ser. No. 705,814, May 24, 1991, abandoned.

L1: 23 of 25

TITLE: Herpes virus thymidien kinase-encoding DNA
US PAT NO: 5,324,664 DATE ISSUED: Jun. 28, 1994
[IMAGE AVAILABLE]
APPL-NO: 08/007,392 DATE FILED: Jan. 21, 1993
REL-US-DATA: Continuation of Ser. No. 646,625, Jan. 28, 1991, abandoned, which is a continuation-in-part of Ser. No. 379,041, Jul. 12, 1989, abandoned, which is a continuation-in-part of Ser. No. 230,158, Aug. 8, 1988, abandoned.

L1: 24 of 25

TITLE: Herpes Simplex virus as a vector
US PAT NO: 5,288,641 DATE ISSUED: Feb. 22, 1994
[IMAGE AVAILABLE]
APPL-NO: 07/923,015 DATE FILED: Jul. 30, 1992
REL-US-DATA: Continuation of Ser. No. 455,771, Dec. 28, 1989, abandoned, which is a continuation of Ser. No. 616,930, Jun. 4, 1984, abandoned.

L1: 25 of 25

TITLE: Recombinant herpes simplex viruses, vaccines and methods
US PAT NO: 4,859,587 DATE ISSUED: Aug. 22, 1989
[IMAGE AVAILABLE]
APPL-NO: 06/856,052 DATE FILED: Apr. 25, 1986
REL-US-DATA: Continuation-in-part of Ser. No. 616,930, Jun. 4, 1984.

=> d l4 1-25 kwic

'L4' NOT FOUND

=> d l1 1-25 kwic

US PAT NO: 5,879,934 [IMAGE AVAILABLE] L1: 1 of 25

SUMMARY:

BSUM(5)

One IE protein, Infected Cell Polypeptide 4 (ICP4), also known as .**alpha.4**, or Vmw175, is absolutely required for both virus infectivity and the transition from IE to later transcription. Owing to its. . . and Shepard, et al., 1991, J. Virol. 65:787-795). Aiding in these studies was the development of a system to grow **herpes** viruses that contain mutations which inactivate essential viral proteins. In this case, cell lines were generated by cotransformation with a. . .

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     (FILE 'USPAT' ENTERED AT 12:19:04 ON 13 JUN 1999)
L1           25 S (ENCEPHALITIS OR ARBOVIRUS OR HERPES)(P)(VLA(W)4 OR ALPH
A(W

=> s (encephalitis or arbovirus or herpes or viral)(P)(vla(w)4)

          1375 ENCEPHALITIS
            87 ARBOVIRUS
          6639 HERPES
         18476 VIRAL
           343 VLA
       2397640 4
L2            8 (ENCEPHALITIS OR ARBOVIRUS OR HERPES OR VIRAL)(P)(VLA(W)4)

=> d l2 1-8 date


                                                          L2: 1 of 8
TITLE:          Treatment for atherosclerosis and other cardiovascular and
                  inflammatory diseases
US PAT NO:      5,846,959                 DATE ISSUED:    Dec. 8, 1998
                [IMAGE AVAILABLE]
APPL-NO:        08/471,537                DATE FILED:     Jun. 6, 1995
REL-US-DATA:    Continuation of Ser. No. 317,399, Oct. 4, 1994, which is a
                  continuation-in-part of Ser. No. 240,858, May 10, 1994,
                  abandoned, which is a continuation-in-part of Ser. No.
                  969,934, Oct. 30, 1992, Pat. No. 5,380,747.

                                                          L2: 2 of 8
TITLE:          Humanized antibodies against leukocyte adhesion molecule
                  VLA-4
US PAT NO:      5,840,299                 DATE ISSUED:    Nov. 24, 1998
                [IMAGE AVAILABLE]
APPL-NO:        08/561,521                DATE FILED:     Nov. 21, 1995
REL-US-DATA:    Continuation-in-part of Ser. No. 186,269, Jan. 25, 1994,
                  abandoned.

                                                          L2: 3 of 8
TITLE:          Treatment for atherosclerosis and other cardiovascular and
                  inflammatory diseases
US PAT NO:      5,811,449                 DATE ISSUED:    Sep. 22, 1998
                [IMAGE AVAILABLE]
APPL-NO:        08/483,335                DATE FILED:     Jun. 7, 1995
REL-US-DATA:    Division of Ser. No. 317,399, Oct. 4, 1994, which is a
                  continuation-in-part of Ser. No. 240,858, May 10, 1994,
                  abandoned, which is a continuation-in-part of Ser. No.
                  969,934, Oct. 30, 1992, Pat. No. 5,380,747.

                                                          L2: 4 of 8
TITLE:          Treatment for atherosclerosis and other cardiovascular and
                  inflammatory diseases
US PAT NO:      5,807,884                 DATE ISSUED:    Sep. 15, 1998
                [IMAGE AVAILABLE]
APPL-NO:        08/317,399                DATE FILED:     Oct. 4, 1994
REL-US-DATA:    Continuation-in-part of Ser. No. 240,858, May 10, 1994,
                  abandoned, which is a continuation-in-part of Ser. No.
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969,934, Oct. 30, 1992, Pat. No. 5,380,747.

L2: 5 of 8

TITLE: Treatment for atherosclerosis and other cardiovascular and inflammatory diseases
US PAT NO: 5,773,231 DATE ISSUED: Jun. 30, 1998
[IMAGE AVAILABLE]
APPL-NO: 08/473,272 DATE FILED: Jun. 7, 1995
REL-US-DATA: Continuation of Ser. No. 317,399, Oct. 4, 1994, which is a continuation-in-part of Ser. No. 240,858, May 10, 1994, abandoned, which is a continuation-in-part of Ser. No. 969,934, Oct. 30, 1992, Pat. No. 5,380,747.

L2: 6 of 8

TITLE: Treatment for atherosclerosis and other cardiovascular and inflammatory diseases
US PAT NO: 5,773,209 DATE ISSUED: Jun. 30, 1998
[IMAGE AVAILABLE]
APPL-NO: 08/484,059 DATE FILED: Jun. 7, 1995
REL-US-DATA: Continuation of Ser. No. 317,399, Oct. 4, 1994, which is a continuation-in-part of Ser. No. 240,858, May 10, 1994, which is a continuation-in-part of Ser. No. 969,934, Oct. 30, 1992, Pat. No. 5,380,747.

L2: 7 of 8

TITLE: Treatment for atherosclerosis and other cardiovascular and inflammatory diseases
US PAT NO: 5,750,351 DATE ISSUED: May 12, 1998
[IMAGE AVAILABLE]
APPL-NO: 08/474,530 DATE FILED: Jun. 7, 1995
REL-US-DATA: Continuation of Ser. No. 317,399, Oct. 4, 1994, which is a continuation-in-part of Ser. No. 240,858, May 10, 1994, abandoned, which is a continuation-in-part of Ser. No. 969,934, Oct. 30, 1992, Pat. No. 5,380,747.

L2: 8 of 8

TITLE: Method for isolating a novel receptor for .alpha.4 integrins
US PAT NO: 5,599,676 DATE ISSUED: Feb. 4, 1997
[IMAGE AVAILABLE]
APPL-NO: 08/323,199 DATE FILED: Oct. 14, 1994
REL-US-DATA: Continuation of Ser. No. 886,992, May 21, 1992, abandoned.

=> d l2 1-8 kwic

US PAT NO: 5,846,959 [IMAGE AVAILABLE] L2: 1 of 8

SUMMARY:

BSUM(3)

Adhesion . . . endothelium represents a fundamental, early event in a wide variety of inflammatory conditions, including atherosclerosis, autoimmune disorders and bacterial and **viral** infections. Leukocyte recruitment to the endothelium is started when inducible adhesion molecule receptors on the surface of endothelial cells interact. . . lesion, there is a localized endothelial expression of VCAM-1 and selective recruitment of mononuclear leukocytes that express the integrin counterreceptor **VLA-4**. Because of the selective expression of **VLA-4** on monocytes and lymphocytes, but not neutrophils, VCAM-1 is important in mediating the selective adhesion of mononuclear leukocytes. Subsequent conversion. . .

US PAT NO: 5,840,299 [IMAGE AVAILABLE] L2: 2 of 8

DETDESC:

DETD(63)

The invention also provides methods of treatment that exploit the capacity of humanized MAb 21.6 to block .alpha.4-dependent interactions of the **VLA-4** receptor. The .alpha.4-dependent interaction of the **VLA-4** receptor with the VCAM-1 ligand on endothelial cells is an early event in many inflammatory responses, particularly those of the. . . include multiple sclerosis (Yednock et al., Nature 356, 63 (1992); Baron et al., J. Exp. Med. 177, 57 (1993)), meningitis, **encephalitis**, stroke, other cerebral traumas, inflammatory bowel disease (Hamann et al., J. Immunol. 152, 3238 (1994)), ulcerative colitis, Crohn's disease, rheumatoid. . .

US PAT NO: 5,811,449 [IMAGE AVAILABLE] L2: 3 of 8

SUMMARY:

BSUM(3)

Adhesion . . . endothelium represents a fundamental, early event in a wide variety of inflammatory conditions, including atherosclerosis, autoimmune disorders and bacterial and **viral** infections. Leukocyte recruitment to the endothelium is started when inducible adhesion molecule receptors on the surface of endothelial cells interact. . . lesion, there is a localized endothelial expression of VCAM-1 and selective recruitment of mononuclear leukocytes that express the integrin counterreceptor **VLA-4**. Because of the selective expression of **VLA-4** on monocytes and lymphocytes, but not neutrophils, VCAM-1 is important in mediating the selective adhesion of mononuclear leukocytes. Subsequent conversion. . .

US PAT NO: 5,807,884 [IMAGE AVAILABLE] L2: 4 of 8

SUMMARY:

BSUM(1)

Adhesion . . . endothelium represents a fundamental, early event in a wide variety of inflammatory conditions, including atherosclerosis, autoimmune disorders and bacterial and **viral** infections. Leukocyte recruitment to the endothelium is started when inducible adhesion molecule receptors on the surface of endothelial cells interact. . . lesion, there is a localized endothelial expression of VCAM-1 and selective recruitment of mononuclear leukocytes that express the integrin counterreceptor **VLA-4**. Because of the selective expression of **VLA-4** on monocytes and lymphocytes, but not neutrophils, VCAM-1 is important in mediating the selective adhesion of mononuclear leukocytes. Subsequent conversion. . .

US PAT NO: 5,773,231 [IMAGE AVAILABLE] L2: 5 of 8

SUMMARY:

BSUM(2)

Adhesion . . . endothelium represents a fundamental, early event in a wide variety of inflammatory conditions, including atherosclerosis, autoimmune disorders and bacterial and **viral** infections. Leukocyte recruitment to the endothelium is started when inducible adhesion molecule receptors on the surface of endothelial cells interact. . . lesion, there is a localized endothelial expression of VCAM-1 and selective recruitment of mononuclear leukocytes that express the integrin

counterreceptor **VLA-4**. Because of the selective expression of **VLA-4** on monocytes and lymphocytes, but not neutrophils, VCAM-1 is important in mediating the selective adhesion of mononuclear leukocytes. Subsequent conversion. . .

US PAT NO: 5,773,209 [IMAGE AVAILABLE] L2: 6 of 8

SUMMARY:

BSUM(3)

Adhesion . . . endothelium represents a fundamental, early event in a wide variety of inflammatory conditions, including atherosclerosis, autoimmune disorders and bacterial and **viral** infections. Leukocyte recruitment to the endothelium is started when inducible adhesion molecule receptors on the surface of endothelial cells interact. . . lesion, there is a localized endothelial expression of VCAM-1 and selective recruitment of mononuclear leukocytes that express the integrin counterreceptor **VLA-4**. Because of the selective expression of **VLA-4** on monocytes and lymphocytes, but not neutrophils, VCAM-1 is important in mediating the selective adhesion of mononuclear leukocytes. Subsequent conversion. . .

US PAT NO: 5,750,351 [IMAGE AVAILABLE] L2: 7 of 8

SUMMARY:

BSUM(2)

Adhesion . . . endothelium represents a fundamental, early event in a wide variety of inflammatory conditions, including atherosclerosis, autoimmune disorders and bacterial and **viral** infections. Leukocyte recruitment to the endothelium is started when inducible adhesion molecule receptors on the surface of endothelial cells interact. . . lesion, there is a localized endothelial expression of VCAM-1 and selective recruitment of mononuclear leukocytes that express the integrin counterreceptor **VLA-4**. Because of the selective expression of **VLA-4** on monocytes and lymphocytes, but not neutrophils, VCAM-1 is important in mediating the selective adhesion of mononuclear leukocytes. Subsequent conversion. . .

US PAT NO: 5,599,676 [IMAGE AVAILABLE] L2: 8 of 8

DETDESC:

DETD(22)

Any . . . in vitro recombinant DNA and synthetic techniques and in vivo recombinants (genetic recombination). Expression of nucleic acid sequence encoding the **VLA-4** Receptor or fragment thereof may be regulated by a second nucleic acid sequence so that the Receptor protein or peptide. . . the promoter contained in the 3' long terminal repeat of Rous sarcoma virus (Yamamoto, et al., 1980, Cell 22:787-797), the **herpes** thymidine kinase promoter (Wagner et al., 1981, Proc. Natl. Acad. Sci. U.S.A. 78:1441-1445), the regulatory sequences of the metallothionein gene. . .

=> s encephalitis(P)(arbovirus or herpes)

```
          1375 ENCEPHALITIS
            87 ARBOVIRUS
          6639 HERPES
L3         456 ENCEPHALITIS(P)(ARBOVIRUS OR HERPES)
```

=> s l3 and vla(w)4

```
          343 VLA
      2397640 4
          134 VLA(W)4
L4          0 L3 AND VLA(W)4

=> s l3(P)(leukocyt? or leucocyt? or lymphocyt?)(P)(inhibit? or suppress? or
antagoni?)

         7994 LEUKOCYT?
         1930 LEUCOCYT?
        13828 LYMPHOCYT?
       273125 INHIBIT?
       132696 SUPPRESS?
        21848 ANTAGONI?
L5          2 L3(P)(LEUKOCYT? OR LEUCOCYT? OR LYMPHOCYT?)(P)(INHIBIT? OR
SUP
              PRESS? OR ANTAGONI?)

=> d l5 1-2 date

                                                          L5: 1 of 2
TITLE:          Transgenic mouse deficient in inducible nitric oxide
                  synthase
US PAT NO:      5,850,004                 DATE,ISSUED:    Dec. 15, 1998
                [IMAGE AVAILABLE]
APPL-NO:        08/808,191                DATE FILED:     Feb. 28, 1997
REL-US-DATA:    Continuation of Ser. No. 284,898, Aug. 2, 1994, abandoned.

                                                          L5: 2 of 2
TITLE:          Restoration of interferon response
US PAT NO:      4,092,425                 DATE ISSUED:    May 30, 1978
                [IMAGE AVAILABLE]
APPL-NO:        05/822,742                DATE FILED:     Aug. 8, 1977

=> d l5 1-2 kwic


US PAT NO:      5,850,004 [IMAGE AVAILABLE]                L5: 1 of 2

SUMMARY:

BSUM(33)

 d. Encephalitis, meningitis, encephalomyelitis: Inflammation within
the central (CNS) and peripheral nervous systems often arises as a
consequence of viral or bacterial. . . (MS). Regardless of origin,
inducible nitric oxide synthase has been associated with several of these
processes. In mice with rabies, lymphocytic choriomeningitis or
herpes simplex viral infections, cerebral expression of iNOS closely
correlates with the incidence and severity of disease (Koprowski et al.,
1993,. . . Koprowski et al., 1993, cited elsewhere herein; Lin et al.,
J. Exp. Med., vol. 178, pp. 643-648). Moreover, the NOS inhibitor
aminoguanidine, ameliorated the course of experimental autoimmune
encephalomyelitis in mice (Cross et al., 1994, J. Clin. Invest., vol. 93,
pp.. . .

US PAT NO:      4,092,425 [IMAGE AVAILABLE]                L5: 2 of 2

SUMMARY:

BSUM(2)

 It . . . Potential limitation to therapeutic use of
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interferon-inducing agents, Infect. Immum., 6: 743 (1972); J. E. Osborn and D. N. Medearis, **Suppression** of Interferon and Antibody and Multiplication of Newcastle Disease Virus in Cytomegalovirus Infected Mice, Proc. Soc. Exp. Biol. Med., 124:. . . Agents Chemother,. Abst. 136, (1974) O. A. Holtermann and E. A. Havell, Reduced interferon response in mice congenially infected with **lymphocytic-** choriomeningitis virus, J. Gen. Viro, 9: 101 (1970) and D. A. Stringfellow et al., **Suppressed** Response to Interferon Induction in Mice Infected with Encephalomyocarditis, Semliki Forest, A.sub.2 Influenza, **Herpes** Hominis Type 2 or Murine Cytomegalo Viruses, J. Infect. Dis., 135:540 (1977). Also, animals exposed to repeated doses of various. . . 42. In Virology Monographs. Springer Verlag. New York., Vilcek, J. and Rada, B. 1962. Studies on an interferon from tickborne **encephalitis** virus infected cells. III Antiviral action on interferon. Acta. Virol. 6:9-16, Youngner, J. S. and Stinebring, W. R. 1965. Interferon. . .

```
=> s (encephalitis)(P)(arbovirus or herpes) and (inhibit? or suppress? or
antagoni? or block?)(P)(lymhocyt? or leukocyt? or leucocyt?)

          1375 ENCEPHALITIS
            87 ARBOVIRUS
          6639 HERPES
           456 (ENCEPHALITIS)(P)(ARBOVIRUS OR HERPES)
        273125 INHIBIT?
        132696 SUPPRESS?
         21848 ANTAGONI?
        780999 BLOCK?
            15 LYMHOCYT?
          7994 LEUKOCYT?
          1930 LEUCOCYT?
          3048 (INHIBIT? OR SUPPRESS? OR ANTAGONI? OR BLOCK?)(P)(LYMHOCYT?
 OR
               LEUKOCYT? OR LEUCOCYT?)
L6          32 (ENCEPHALITIS)(P)(ARBOVIRUS OR HERPES) AND (INHIBIT? OR SUP
PRE
               SS? OR ANTAGONI? OR BLOCK?)(P)(LYMHOCYT? OR LEUKOCYT? OR LE
UCO
               CYT?)

=> d l6 1-32 date

                                                          L6: 1 of 32
TITLE:          Polyethylene glycol modified interferon therapy
US PAT NO:      5,908,621                 DATE ISSUED:    Jun. 1, 1999
                [IMAGE AVAILABLE]
APPL-NO:        08/839,101                DATE FILED:     Apr. 29, 1997
REL-US-DATA:    Continuation-in-part of Ser. No. 742,305, Nov. 1, 1996.

                                                          L6: 2 of 32
TITLE:          Method of determining DNA sequence preference of a
                  DNA-binding molecule
US PAT NO:      5,869,241                 DATE ISSUED:    Feb. 9, 1999
                [IMAGE AVAILABLE]
APPL-NO:        08/475,228                DATE FILED:     Jun. 7, 1995
REL-US-DATA:    Division of Ser. No. 171,389, Dec. 20, 1993, Pat. No.
                  5,578,444, which is a continuation-in-part of Ser. No.
                  123,936, Sep. 17, 1993, Pat. No. 5,726,014, which is a
                  continuation-in-part of Ser. No. 996,783, Dec. 23, 1992,
                  Pat. No. 5,693,463, which is a continuation-in-part of
                  Ser. No. 723,618, Jun. 27, 1991, abandoned.

                                                          L6: 3 of 32
TITLE:          Guanylhydrazones and their use to treat inflammatory
                  conditions
US PAT NO:      5,854,289                 DATE ISSUED:    Dec. 29, 1998
                [IMAGE AVAILABLE]
APPL-NO:        08/632,305                DATE FILED:     Apr. 15, 1996
REL-US-DATA:    Division of Ser. No. 463,568, Jun. 5, 1995, Pat. No.
                  5,750,573, which is a continuation-in-part of Ser. No.
                  315,170, Sep. 29, 1994, Pat. No. 5,599,984, which is a
                  continuation-in-part of Ser. No. 184,540, Jan. 21, 1994,
                  abandoned.
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L6: 4 of 32

TITLE: Transgenic mouse deficient in inducible nitric oxide synthase

US PAT NO: 5,850,004 [IMAGE AVAILABLE] DATE ISSUED: Dec. 15, 1998

APPL-NO: 08/808,191 DATE FILED: Feb. 28, 1997

REL-US-DATA: Continuation of Ser. No. 284,898, Aug. 2, 1994, abandoned.

L6: 5 of 32

TITLE: Uses of aloe products in the treatment of chronic respiratory diseases

US PAT NO: 5,786,342 [IMAGE AVAILABLE] DATE ISSUED: Jul. 28, 1998

APPL-NO: 08/462,821 DATE FILED: Jun. 5, 1995

REL-US-DATA: Division of Ser. No. 159,830, Dec. 1, 1993, Pat. No. 5,441,943, which is a division of Ser. No. 864,583, Apr. 7, 1992, Pat. No. 5,308,838, which is a division of Ser. No. 558,905, Jul. 27, 1990, Pat. No. 5,118,673, which is a continuation-in-part of Ser. No. 229,164, Aug. 5, 1988, Pat. No. 5,106,616, which is a continuation-in-part of Ser. No. 144,872, Jan. 14, 1988, Pat. No. 4,851,224, which is a continuation-in-part of Ser. No. 869,261, Jun. 5, 1986, Pat. No. 4,735,935, which is a continuation-in-part of Ser. No. 810,025, Dec. 17, 1985, abandoned, which is a continuation-in-part of Ser. No. 754,859, Jul. 12, 1985, abandoned, which is a continuation-in-part of Ser. No. 750,321, Jun. 28, 1985, abandoned, which is a continuation-in-part of Ser. No. 649,967, Sep. 12, 1984, abandoned, which is a continuation of Ser. No. 375,720, May 7, 1982, abandoned.

L6: 6 of 32

TITLE: Uses of aloe products in the treatment of multiple sclerosis

US PAT NO: 5,780,453 [IMAGE AVAILABLE] DATE ISSUED: Jul. 14, 1998

APPL-NO: 08/464,550 DATE FILED: Jun. 5, 1995

REL-US-DATA: Division of Ser. No. 159,830, Dec. 1, 1993, Pat. No. 5,441,943, which is a division of Ser. No. 864,583, Apr. 7, 1992, Pat. No. 5,308,838, which is a division of Ser. No. 558,905, Jul. 27, 1990, Pat. No. 5,118,673, which is a continuation-in-part of Ser. No. 229,164, Aug. 5, 1988, Pat. No. 5,106,616, which is a continuation-in-part of Ser. No. 144,872, Jan. 14, 1988, Pat. No. 4,851,224, Jul. 25, 1989, which is a continuation-in-part of Ser. No. 869,261, Jun. 5, 1986, Pat. No. 4,735,935, Apr. 5, 1988, which is a continuation-in-part of Ser. No. 810,025, Dec. 17, 1985, abandoned, which is a continuation-in-part of Ser. No. 754,859, Jul. 12, 1985, abandoned, which is a continuation-in-part of Ser. No. 750,321, Jun. 28, 1985, abandoned, which is a continuation-in-part of Ser. No. 649,967, Sep. 12, 1984, abandoned, which is a continuation of Ser. No. 375,720, May 7, 1982, abandoned.

L6: 7 of 32

TITLE: Antineoplastic uses of aloe products

US PAT NO: 5,773,425 [IMAGE AVAILABLE] DATE ISSUED: Jun. 30, 1998

APPL-NO: 08/463,202 DATE FILED: Jun. 5, 1995

REL-US-DATA: Division of Ser. No. 159,830, Dec. 1, 1993, Pat. No. 5,441,943, which is a division of Ser. No. 864,583, Apr. 7, 1992, Pat. No. 5,308,838, which is a division of Ser.

No. 558,905, Jul. 27, 1990, Pat. No. 5,118,673, which is a continuation-in-part of Ser. No. 229,164, Aug. 5, 1988, Pat. No. 5,106,616, which is a continuation-in-part of Ser. No. 144,872, Jan. 14, 1988, Pat. No. 4,851,224, Jul. 25, 1989, which is a continuation-in-part of Ser. No. 869,261, Jun. 5, 1986, Pat. No. 4,735,935, Apr. 5, 1988, which is a continuation-in-part of Ser. No. 810,025, Dec. 17, 1985, abandoned, which is a continuation-in-part of Ser. No. 754,859, Jul. 12, 1985, abandoned, which is a continuation-in-part of Ser. No. 750,321, Jun. 28, 1985, abandoned, which is a continuation-in-part of Ser. No. 649,967, Sep. 12, 1984, abandoned, which is a continuation of Ser. No. 375,720, May 7, 1982, abandoned.

L6: 8 of 32

TITLE: Sequence-directed DNA-binding molecules compositions and methods

US PAT NO: 5,744,131 DATE ISSUED: Apr. 28, 1998
[IMAGE AVAILABLE]

APPL-NO: 08/476,876 DATE FILED: Jun. 7, 1995

REL-US-DATA: Division of Ser. No. 996,783, Dec. 23, 1992, which is a continuation-in-part of Ser. No. 723,618, Jun. 27, 1991, abandoned.

L6: 9 of 32

TITLE: Sequence-directed DNA-binding molecules compositions and methods

US PAT NO: 5,738,990 DATE ISSUED: Apr. 14, 1998
[IMAGE AVAILABLE]

APPL-NO: 08/475,221 DATE FILED: Jun. 7, 1995

REL-US-DATA: Division of Ser. No. 996,783, Dec. 23, 1992, which is a continuation-in-part of Ser. No. 723,618, Jun. 27, 1991, abandoned.

L6: 10 of 32

TITLE: Screening assay for the detection of DNA-binding molecules

US PAT NO: 5,726,014 DATE ISSUED: Mar. 10, 1998
[IMAGE AVAILABLE]

APPL-NO: 08/123,936 DATE FILED: Sep. 17, 1993

REL-US-DATA: Continuation-in-part of Ser. No. 996,783, Dec. 23, 1992, which is a continuation-in-part of Ser. No. 723,618, Jun. 27, 1991, abandoned.

L6: 11 of 32

TITLE: Compositions and methods for use of IL-12 as an adjuvant

US PAT NO: 5,723,127 DATE ISSUED: Mar. 3, 1998
[IMAGE AVAILABLE]

APPL-NO: 08/621,493 DATE FILED: Mar. 25, 1996

REL-US-DATA: Division of Ser. No. 265,087, Jun. 17, 1994, Pat. No. 5,571,515, which is a continuation-in-part of Ser. No. 229,282, Apr. 18, 1994, abandoned.

L6: 12 of 32

TITLE: Method of constructing sequence-specific DNA-binding molecules

US PAT NO: 5,716,780 DATE ISSUED: Feb. 10, 1998
[IMAGE AVAILABLE]

APPL-NO: 08/484,499 DATE FILED: Jun. 7, 1995

REL-US-DATA: Division of Ser. No. 996,783, Dec. 23, 1992, which is a continuation-in-part of Ser. No. 723,618, Jun. 27, 1991, abandoned.

L6: 13 of 32

TITLE: Uses of aloe products in the prevention and treatment of infections and infestations

US PAT NO: 5,703,060 DATE ISSUED: Dec. 30, 1997
[IMAGE AVAILABLE]

APPL-NO: 08/463,019 DATE FILED: Jun. 5, 1995

REL-US-DATA: Division of Ser. No. 159,830, Dec. 1, 1993, Pat. No. 5,441,943, which is a division of Ser. No. 864,583, Apr. 7, 1992, Pat. No. 5,308,838, which is a division of Ser. No. 558,905, Jul. 27, 1990, Pat. No. 5,118,673, which is a continuation-in-part of Ser. No. 229,164, Aug. 5, 1988, Pat. No. 5,106,616, which is a continuation-in-part of Ser. No. 144,872, Jan. 14, 1988, Pat. No. 4,851,224, Jul. 25, 1989, which is a continuation-in-part of Ser. No. 869,261, Jun. 5, 1986, Pat. No. 4,735,935, Apr. 5, 1988, which is a continuation-in-part of Ser. No. 810,025, Dec. 17, 1985, abandoned, which is a continuation-in-part of Ser. No. 754,859, Jul. 12, 1985, abandoned, which is a continuation-in-part of Ser. No. 750,321, Jun. 28, 1985, abandoned, which is a continuation-in-part of Ser. No. 649,967, Sep. 12, 1984, abandoned, which is a continuation of Ser. No. 375,720, May 7, 1982, abandoned.

L6: 14 of 32

TITLE: Method of ordering sequence binding preferences of a DNA-binding molecule

US PAT NO: 5,693,463 DATE ISSUED: Dec. 2, 1997
[IMAGE AVAILABLE] DISCL-DATE: Apr. 26, 2011

APPL-NO: 07/996,783 DATE FILED: Dec. 23, 1992

REL-US-DATA: Continuation-in-part of Ser. No. 723,618, Jun. 27, 1991, abandoned.

L6: 15 of 32

TITLE: Bioadhesive-wound healing compositions and methods for preparing and using same

US PAT NO: 5,658,956 DATE ISSUED: Aug. 19, 1997
[IMAGE AVAILABLE]

APPL-NO: 08/445,824 DATE FILED: May 22, 1995

REL-US-DATA: Continuation-in-part of Ser. No. 298,521, Aug. 30, 1994, abandoned, which is a continuation-in-part of Ser. No. 53,922, Apr. 26, 1993, abandoned, which is a continuation of Ser. No. 663,500, Mar. 1, 1991, abandoned.

L6: 16 of 32

TITLE: Causative agent of the mystery swine disease, vaccine compositions and diagnostic kits

US PAT NO: 5,620,691 DATE ISSUED: Apr. 15, 1997
[IMAGE AVAILABLE]

APPL-NO: 08/157,005 DATE FILED: Nov. 26, 1993
FRN-PR. NO: 91201398 FRN FILED: Jun. 6, 1991
FRN-PR. CO: European Patent Office
FRN-PR. NO: 92200781 FRN FILED: Mar. 18, 1992
FRN-PR. CO: European Patent Office
PCT-NO: PCT/NL92/00096 PCT-FILED: Jun. 5, 1992
371-DATE: Nov. 26, 1993
102(E)-DATE: Nov. 26, 1993
PCT-PUB-NO: WO92/21375 PCT-PUB-DATE: Dec. 10, 1992

L6: 17 of 32

TITLE: Uses of aloe products in the treatment of inflammatory diseases

US PAT NO: 5,587,364 DATE ISSUED: Dec. 24, 1996
[IMAGE AVAILABLE]

APPL-NO: 08/462,972 DATE FILED: Jun. 5, 1995
REL-US-DATA: Division of Ser. No. 159,830, Dec. 1, 1993, Pat. No. 5,441,943, which is a division of Ser. No. 864,583, Apr. 7, 1992, Pat. No. 5,308,838, which is a division of Ser. No. 558,905, Jul. 27, 1990, Pat. No. 5,118,673, which is a continuation-in-part of Ser. No. 229,164, Aug. 5, 1988, Pat. No. 5,106,616, which is a continuation-in-part of Ser. No. 144,872, Jan. 14, 1988, Pat. No. 4,851,224, Jul. 25, 1989, which is a continuation-in-part of Ser. No. 869,261, Jun. 5, 1986, Pat. No. 4,735,935, Apr. 5, 1988, which is a continuation-in-part of Ser. No. 810,025, Dec. 17, 1985, abandoned, which is a continuation-in-part of Ser. No. 754,859, Jul. 12, 1985, abandoned, which is a continuation-in-part of Ser. No. 750,321, Jun. 28, 1985, abandoned, which is a continuation-in-part of Ser. No. 649,967, Sep. 12, 1984, abandoned, which is a continuation of Ser. No. 375,720, May 7, 1982, abandoned.

L6: 18 of 32

TITLE: Sequence-directed DNA-binding molecules compositions and methods
US PAT NO: 5,578,444 DATE ISSUED: Nov. 26, 1996
[IMAGE AVAILABLE]
APPL-NO: 08/171,389 DATE FILED: Dec. 20, 1993
REL-US-DATA: Continuation-in-part of Ser. No. 123,936, Sep. 17, 1993, which is a continuation-in-part of Ser. No. 996,783, Dec. 23, 1992, which is a continuation-in-part of Ser. No. 723,618, Jun. 27, 1991, abandoned.

L6: 19 of 32

TITLE: Compositions and methods for use of IL-12 as an adjuvant
US PAT NO: 5,571,515 DATE ISSUED: Nov. 5, 1996
[IMAGE AVAILABLE]
APPL-NO: 08/265,087 DATE FILED: Jun. 17, 1994
REL-US-DATA: Continuation-in-part of Ser. No. 229,282, Apr. 18, 1994, abandoned.

L6: 20 of 32

TITLE: Uses of aloe products
US PAT NO: 5,441,943 DATE ISSUED: Aug. 15, 1995
[IMAGE AVAILABLE]
APPL-NO: 08/159,830 DATE FILED: Dec. 1, 1993
REL-US-DATA: Division of Ser. No. 864,583, Apr. 7, 1992, Pat. No. 5,308,838, which is a division of Ser. No. 558,905, Jul. 27, 1990, Pat. No. 5,118,673, which is a continuation-in-part of Ser. No. 229,164, Aug. 5, 1988, Pat. No. 5,106,616, which is a continuation-in-part of Ser. No. 144,872, Jan. 14, 1988, Pat. No. 4,851,224, Jul. 25, 1989, which is a continuation-in-part of Ser. No. 869,261, Jun. 5, 1986, Pat. No. 4,735,935, Apr. 5, 1988, which is a continuation-in-part of Ser. No. 810,025, Dec. 17, 1985, abandoned, which is a continuation-in-part of Ser. No. 754,859, Jul. 12, 1985, abandoned, which is a continuation-in-part of Ser. No. 750,321, Jun. 28, 1985, abandoned, which is a continuation-in-part of Ser. No. 649,967, Sep. 12, 1984, abandoned, which is a continuation of Ser. No. 375,720, May 7, 1982, abandoned.

L6: 21 of 32

TITLE: Uses of aloe products
US PAT NO: 5,308,838 DATE ISSUED: May 3, 1994
[IMAGE AVAILABLE]

APPL-NO: 07/864,583 DATE FILED: Apr. 7, 1992
REL-US-DATA: Division of Ser. No. 558,905, Jul. 27, 1990, Pat. No. 5,118,673, which is a continuation-in-part of Ser. No. 229,164, Aug. 5, 1988, Pat. No. 5,106,616, which is a continuation-in-part of Ser. No. 144,872, Jan. 14, 1988, Pat. No. 4,851,224, Jul. 25, 1989, which is a continuation-in-part of Ser. No. 869,261, Jun. 5, 1986, Pat. No. 4,735,935, Apr. 5, 1988, which is a continuation-in-part of Ser. No. 810,025, Dec. 17, 1985, abandoned, which is a continuation-in-part of Ser. No. 754,859, Jul. 12, 1985, abandoned, which is a continuation-in-part of Ser. No. 750,321, Jun. 28, 1985, abandoned, which is a continuation-in-part of Ser. No. 649,967, Sep. 12, 1984, abandoned, which is a continuation of Ser. No. 375,720, May 7, 1982, abandoned.

L6: 22 of 32

TITLE: Method of **inhibiting** the activity of **leukocyte** derived cytokines
US PAT NO: 5,272,153 DATE ISSUED: Dec. 21, 1993
[IMAGE AVAILABLE] DISCL-DATE: Jun. 15, 2008
APPL-NO: 07/908,929 DATE FILED: Jul. 2, 1992
REL-US-DATA: Continuation of Ser. No. 700,522, May 15, 1991, abandoned, which is a continuation of Ser. No. 622,138, Dec. 5, 1990, Pat. No. 5,096,906, which is a continuation of Ser. No. 508,535, Apr. 11, 1990, abandoned, which is a continuation of Ser. No. 239,761, Sep. 2, 1988, abandoned, which is a continuation of Ser. No. 947,905, Dec. 31, 1986, abandoned, and a continuation of Ser. No. 131,785, Dec. 11, 1987, Pat. No. 4,965,271.

L6: 23 of 32

TITLE: Method of **inhibiting** the activity of **leukocyte** derived cytokines
US PAT NO: 5,196,430 DATE ISSUED: Mar. 23, 1993
[IMAGE AVAILABLE] DISCL-DATE: Oct. 23, 2007
APPL-NO: 07/762,200 DATE FILED: Sep. 18, 1991
REL-US-DATA: Division of Ser. No. 622,138, Dec. 5, 1990, Pat. No. 5,096,906, which is a continuation of Ser. No. 508,535, Apr. 11, 1990, abandoned, which is a continuation of Ser. No. 239,761, Sep. 2, 1988, abandoned, which is a continuation of Ser. No. 947,905, Dec. 31, 1986, abandoned, which is a continuation of Ser. No. 131,785, Dec. 11, 1987, Pat. No. 4,965,271, which is a continuation-in-part of Ser. No. 947,905, Dec. 31, 1986, abandoned.

L6: 24 of 32

TITLE: Method of **inhibiting** the activity of **leukocyte** derived cytokines
US PAT NO: 5,196,429 DATE ISSUED: Mar. 23, 1993
[IMAGE AVAILABLE]
APPL-NO: 07/738,096 DATE FILED: Jul. 30, 1991
REL-US-DATA: Continuation of Ser. No. 622,138, Dec. 5, 1990, Pat. No. 5,096,906, which is a continuation of Ser. No. 508,535, Apr. 11, 1990, abandoned, which is a continuation of Ser. No. 239,761, Sep. 2, 1988, abandoned, which is a continuation of Ser. No. 947,905, Dec. 31, 1986, abandoned, and a continuation of Ser. No. 131,785, Dec. 11, 1987, Pat. No. 4,965,271, which is a continuation-in-part of Ser. No. 947,905, Dec. 31, 1986.

L6: 25 of 32

TITLE: Diequatorially bound .beta.-1, 4 polyuronates and use of

same for cytokine stimulation

US PAT NO: 5,169,840 DATE ISSUED: Dec. 8, 1992
[IMAGE AVAILABLE]
APPL-NO: 07/676,103 DATE FILED: Mar. 27, 1991

L6: 26 of 32

TITLE: Uses of aloe products
US PAT NO: 5,118,673 DATE ISSUED: Jun. 2, 1992
[IMAGE AVAILABLE]
APPL-NO: 07/558,905 DATE FILED: Jul. 27, 1990
REL-US-DATA: Continuation-in-part of Ser. No. 229,164, Aug. 5, 1988, which is a continuation-in-part of Ser. No. 144,872, Jan. 14, 1988, Pat. No. 4,851,224, which is a continuation-in-part of Ser. No. 867,261, Jun. 5, 1986, Pat. No. 4,735,935, which is a continuation-in-part of Ser. No. 810,025, Dec. 17, 1985, abandoned, which is a continuation-in-part of Ser. No. 754,859, Jul. 12, 1985, abandoned, which is a continuation-in-part of Ser. No. 750,321, Jun. 28, 1985, abandoned, which is a continuation-in-part of Ser. No. 649,967, Sep. 12, 1984, abandoned, which is a continuation of Ser. No. 375,720, May 7, 1982.

L6: 27 of 32

TITLE: Administration of acemannan
US PAT NO: 5,106,616 DATE ISSUED: Apr. 21, 1992
[IMAGE AVAILABLE]
APPL-NO: 07/229,164 DATE FILED: Aug. 5, 1988
REL-US-DATA: Continuation-in-part of Ser. No. 144,872, Jan. 14, 1988, Pat. No. 4,851,224, which is a continuation-in-part of Ser. No. 869,261, Jun. 5, 1986, Pat. No. 4,735,935, Apr. 5, 1988, which is a continuation-in-part of Ser. No. 810,025, Dec. 17, 1985, abandoned, which is a continuation-in-part of Ser. No. 754,859, Jul. 12, 1985, abandoned, which is a continuation-in-part of Ser. No. 750,321, Jun. 28, 1985, abandoned, which is a continuation-in-part of Ser. No. 649,967, Sep. 12, 1984, abandoned, which is a continuation of Ser. No. 375,720, May 7, 1982, abandoned.

L6: 28 of 32

TITLE: Method of **inhibiting** the activity of **leukocyte** derived cytokines
US PAT NO: 5,096,906 DATE ISSUED: Mar. 17, 1992
[IMAGE AVAILABLE] DISCL-DATE: Oct. 23, 2007
APPL-NO: 07/622,138 DATE FILED: Dec. 5, 1990
REL-US-DATA: Continuation of Ser. No. 508,535, Apr. 11, 1990, abandoned, which is a continuation of Ser. No. 239,761, Sep. 2, 1988, abandoned, which is a continuation of Ser. No. 947,905, Dec. 31, 1986, abandoned, and a continuation of Ser. No. 131,785, Dec. 11, 1987, Pat. No. 4,965,271, which is a continuation-in-part of Ser. No. 947,905, Dec. 31, 1986, abandoned.

L6: 29 of 32

TITLE: Method of **inhibiting** the activity of **leukocyte** derived cytokines
US PAT NO: 4,965,271 DATE ISSUED: Oct. 23, 1990
[IMAGE AVAILABLE]
APPL-NO: 07/131,785 DATE FILED: Dec. 11, 1987
REL-US-DATA: Continuation-in-part of Ser. No. 947,905, Dec. 31, 1986, abandoned.

L6: 30 of 32

TITLE: Low molecular weight complex of polyriboinosinic-

polyribocytidylic acid and method of inducing interferon
US PAT NO: 4,389,395 DATE ISSUED: Jun. 21, 1983
[IMAGE AVAILABLE]
APPL-NO: 06/223,881 DATE FILED: Jan. 9, 1981

L6: 31 of 32

TITLE: Interferon product and process for its preparation
US PAT NO: 4,273,703 DATE ISSUED: Jun. 16, 1981
[IMAGE AVAILABLE]
APPL-NO: 05/955,389 DATE FILED: Oct. 27, 1978
FRN-PR. NO: 4859/77 FRN FILED: Nov. 1, 1977
FRN-PR. CO: Denmark

L6: 32 of 32

TITLE: Method of alleviating diseases by cell-mediated immune modulation
US PAT NO: 4,215,137 DATE ISSUED: Jul. 29, 1980
[IMAGE AVAILABLE]
APPL-NO: 05/919,224 DATE FILED: Jun. 26, 1978

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US PAT NO: 5,272,153 [IMAGE AVAILABLE] L6: 22 of 32
TITLE: Method of **inhibiting** the activity of **leukocyte** derived cytokines

ABSTRACT:
A family of compounds effective in **inhibiting** interleukin-1 (IL-1) activity, tumor necrosis factor (TNF) activity, and the activity of other **leukocyte** derived cytokines is comprised of 7-(oxoalkyl) 1,3-dialkyl xanthines of the formula ##STR1## in which R.sub.1 and R.sub.2 are the same. . . . carbon atoms which can be substituted by a methyl group. Another family of effective compounds is identified as ##STR2## The **inhibition** of IL-1, TNF, and other cytokines in mammals is implicated in alleviation of a wide variety of disease conditions.

SUMMARY:

BSUM(2)

This invention relates to the **inhibition** of activity of **leukocyte** derived cytokines, such as interleukin-1 and tumor necrosis factor, in humans and mammals. More specifically, this invention provides a method of **inhibiting** the activity of cytokines to arrest or alleviate certain disease and inflammatory states.

SUMMARY:

BSUM(3)

Interleukin-1 . . . wide variety of cells and tissues, both in vitro and in vivo. Research has demonstrated that IL-1, TNF, and other **leukocyte** derived cytokines are important, and even critical, mediators in a wide variety of inflammatory states and diseases. The **inhibition** of IL-1, TNF, and other **leukocyte** derived cytokines is of benefit in controlling, reducing, and alleviating many of these conditions.

SUMMARY:

BSUM(4)

Detection and **inhibition** of IL-1, TNF, and other **leukocyte** derived cytokines can be relatively easily documented through in vitro

analysis of polymorphonuclear neutrophil behavior. Among other activities attributed to IL-1 and other **leukocyte** derived cytokines is the promotion of **leukocyte** adherence and the **inhibition** of neutrophil chemotaxis, both directly contributing to disease and inflammation syndromes.

SUMMARY:

BSUM(5)

Despite the desirability of **inhibiting** the activity of IL-1 and TNF and the activity of other **leukocyte** derived cytokines and the ease with which **inhibition** can be detected in vitro, there exists a need in the art for **inhibitors** of IL-1, TNF, and other cytokines, wherein the **inhibitors** are acceptable for in vivo administration.

SUMMARY:

BSUM(7)

This . . . class of compounds that can be successfully employed in alleviating conditions caused by, or mediated by, IL-1, TNF, and other **leukocyte** derived cytokines. The compounds exhibit marked **inhibition** of cytokine activity, even at low concentrations of the mediators as demonstrated through in vitro tests.

SUMMARY:

BSUM(8)

More particularly, this invention provides a method of **inhibiting** the activity of IL-1, TNF, and other **leukocyte** derived cytokines in a mammal comprising administering thereto at least one 7-(oxoalkyl) 1,3-dialkyl xanthine of the formula (I) ##STR3## in. . .

SUMMARY:

BSUM(10)

a . . . 4 carbon atoms. The xanthine of formula (I) or formula (II) is employed in an amount that is effective in **inhibiting** the activity of IL-1, TNF, and other **leukocyte** derived cytokines in the mammal.

SUMMARY:

BSUM(11)

Exemplary within the general formula (II), and established as an effective IL-1 **inhibitor**, is the well known and commercially available pharmaceutical pentoxifylline. Although this compound has been used for some time as a pharmaceutical (clinical trials in 1971) it has not been reported effective as an IL-1 **inhibitor**. It has been demonstrated in promoting directed migration of **leukocytes**.

DETDESC:

DETD(2)

Inhibition of the activity of IL-1, TNF, and other **leukocyte** derived cytokines can be achieved by the administration of xanthines of formula (I) or formula (II) to a mammal.

DETDESC:

DETD(4)

The term "cytokine" as used herein means a secretory product of a **leukocyte**, and in particular a non-antibody protein released by a **leukocyte** on contact with antigen and which acts as an intercellular mediator of immune response. Examples of cytokines that are within the scope of this invention are chemotactic factors, factors promoting replication of lymphocytes, factors **inhibiting** replication of lymphocytes, factors affecting macrophage adherence, factors affecting enzyme secretion by macrophages, and factors that mediate secretion of oxidizing. . .

DETDESC:

DETD(6)

A compound that has been found to be particularly effective for **inhibiting** the effects of IL-1 and other **leukocyte** derived cytokines on polymorphonuclear **leukocytes** and monocytes is 1,3-dibutyl 7-(2-oxopropyl) xanthine. This compound, which is also referred to herein in abbreviated form as "DBOPX", has the following formula: ##STR8## The ability of compound (III) to **inhibit** the effects of IL-1 and other **leukocyte** derived cytokines on polymorphonuclear **leukocyte** and monocyte adherence, cell chemotaxis, respiratory (metabolic) burst, and cell degranulation has been demonstrated and is described hereinafter.

DETDESC:

DETD(22)

Leukocyte response to an acute inflammatory stimulus involves a complex series of events, including adherence to endothelium near the stimulus. **Inhibition** of **leukocyte** adherence can be expected to reduce the degree of inflammation seen in conditions, such a septic shock and adult respiratory distress syndrome. It has been found that the 7-(oxoalkyl) 1,3-dialkyl xanthines employed in this invention effectively **block** adherence of polymorphonuclear **leukocytes**.

DETDESC:

DETD(24)

FIG. . . . However, when DBOPX was included in the assay at concentrations above about 0.1 (.mu.g/ml) PMN adherence to the nylon was **inhibited** as evidenced by a decline in percent adherence. At a DBOPX concentration of 10 (.mu.g/ml) the percent PMN adherence declined. . . incubated with conditioned medium was 99.7%. Thus, the compounds employed in the process of this invention are particularly effective in **blocking** adherence of **leukocytes** and thereby aiding in reducing the degree of inflammation.

DETDESC:

DETD(35)

Referring to FIG. 7, lysozyme released by PMN primed with LPS-stimulated mononuclear **leukocyte** conditioned medium (containing inflammatory cytokines) and stimulated with FMLP was about 2.1 .mu.g/ml in the absence of DBOPX. When DBOPX. . . .mu.g/ml. At a DBOPX concentration of 100 .mu.g/ml, the lysozyme release was only about 1.04 .mu.g/ml. The probability that DBOPX **inhibited** lysozyme release from PMN primed with conditioned medium and stimulated with FMLP was 95%.

DETDESC:

DETD(37)

In summary, the compounds of formula (I) employed in the process of this invention are capable of modulating the effects of **leukocyte** derived cytokines, such as interleukin-1 and tumor necrosis factor, on phagocytes, such as polymorphonuclear **leukocytes**. The compounds are capable of substantially aiding chemotaxis. In addition, the compounds can **block** adherence of cells. The compounds can decrease oxidative damage to host tissues by phagocytes as evidenced by modulation of respiratory burst in stimulated polymorphonuclear **leukocytes**. Finally, the compounds can modulate the effects of cytokines on degranulation in stimulated phagocytes. The demonstrated **inhibition** of IL-1, TNF, and other cytokines by these compounds is suggestive of clinical effectiveness in at least the following areas. . .

DETDESC:

DETD(38)

Because IL-1, TNF, and other **leukocyte** derived cytokines have been implicated in such a wide variety of mammalian conditions, this invention has a similarly broad scope of application. Among the conditions that can be treated or alleviated by the **inhibition** of IL-1, TNF, and other **leukocyte** derived cytokines are: sepsis, septic shock, endotoxic shock, gram negative sepsis, toxic shock syndrome, adult respiratory distress, fever and myalgias. . .

DETDESC:

DETD(42)

Representative viruses are: Rhinovirus; Parainfluenza; Enterovirus; Influenza; Smallpox and vaccinia; **Herpes** simplex; Measles; Rubella; **Arbovirus** (Western, Eastern and Venezuelan equine **encephalitis**, and California **encephalitis**); Rabies; Colorado tick fever; Yellow fever; Dengue; Hepatitis Virus B (HB Ag); Hepatitis Virus A (HAV); and Human Immunodeficiency Virus. . . .

DETDESC:

DETD(46)

In addition, **inhibition** of IL-1, TNF, and other **leukocyte** derived cytokines will enhance phagocyte activity in stored blood and blood products.

DETDESC:

DETD(120)

To demonstrate the effectiveness of the claimed invention, a compound of the general formula (I) was tested to demonstrate **inhibition** of the activity of both in vitro-generated human IL-1 and other leakocyte derived cytokines, and purified human IL-1. Though a variety of compounds within the general formula (I) are effective in **inhibiting** the activities of IL-1 and other **leukocyte** derived cytokines, they will be exemplified with regard to 1,3-dibutyl 7-(2-oxopropyl)xanthine (DBPOX) as a particularly preferred form of the invention.

DETDESC:

DETD(133)

DBOPX increased chemotaxis **inhibited** by IL-1, TNF, or LPS stimulated mononuclear **leukocyte** conditioned medium as shown in FIGS. 1, 2 and

CLAIMS:

CLMS(1)

What is claimed is:

1. A method of **inhibiting** immune response in a mammal, wherein the method comprises administering to the mammal an amount of at least one 7-(oxoalkyl). . .
with up to 4 carbon atoms, which can be substituted by a methyl group; and
wherein said amount is effective in **inhibiting** immune response by **inhibiting** the activity of IL-1, TNF, or other **leukocyte** derived cytokines on polymorphonuclear **leukocytes**.

CLAIMS:

CLMS(2)

2. A method of **inhibiting** immune response in a mammal, wherein the method comprises administering to the mammal an amount of at least one 7-(oxoalkyl). . .
with up to 4 carbon atoms, which can be substituted by a methyl group; and
wherein said amount is effective in **inhibiting** immune response by **inhibiting** the activity of IL-1, TNF, or other **leukocyte** derived cytokines on neutrophils.

CLAIMS:

CLMS(3)

3. A method of **inhibiting** immune response in a mammal, wherein the method comprises administering to the mammal an amount of at least one 7-(oxoalkyl). . .
with up to 4 carbon atoms, which can be substituted by a methyl group; and
wherein said amount is effective in **inhibiting** immune response by **inhibiting** the activity of IL-1, TNF, or other **leukocyte** derived cytokines on mononuclear phagocytes.

CLAIMS:

CLMS(4)

4. A method of **inhibiting** immune response in a mammal, wherein the method comprises administering to the mammal an amount of at least one 7-(oxoalkyl). . .
with up to 4 carbon atoms, which can be substituted by a methyl group; and
wherein said amount is effective in **inhibiting** immune response by **inhibiting** the activity of IL-1, TNF, or other **leukocyte** derived cytokines on monocytes.

CLAIMS:

CLMS(5)

5. A method of **inhibiting** immune response in a mammal, wherein the method comprises administering to the mammal an amount of at least one 7-(oxoalkyl). . .
with up to 4 carbon atoms, which can be substituted by a methyl group; and

wherein said amount is effective in **inhibiting** immune response by **inhibiting** the activity of IL-1, TNF, or other **leukocyte** derived cytokines on macrophages.

CLAIMS:

CLMS(6)

6. A method of **inhibiting** immune response in a mammal, wherein the method comprises administering to the mammal an amount of at least one 7-(oxoalkyl). . .
with up to 4 carbon atoms, which can be substituted by a methyl group; and
wherein said amount is effective in **inhibiting** immune response by **inhibiting** the activity of IL-1, TNF, or other **leukocyte** derived cytokines on lymphocytes.

CLAIMS:

CLMS(8)

8. A method of **inhibiting** immune response in a mammal, wherein the method comprises administering to the mammal an amount of at least one xanthine. . .
R.sup.1 or R.sup.3 being as defined above, and R.sup.2 is a C.sub.1 -C.sub.4 alkyl group;
wherein said amount is effective in **inhibiting** immune response by **inhibiting** the activity of IL-1, TNF, or other **leukocyte** derived cytokines on polymorphonuclear **leukocytes**.

CLAIMS:

CLMS(9)

9. A method of **inhibiting** immune response in a mammal, wherein the method comprises administering to the mammal, an amount of at least one xanthine. . .
R.sup.1 or R.sup.3 being as defined above, and R.sup.2 is a C.sub.1 -C.sub.4 alkyl group;
wherein said amount is effective in **inhibiting** immune response by **inhibiting** the activity of IL-1, TNF, or other **leukocyte** derived cytokines on neutrophils.

CLAIMS:

CLMS(10)

10. A method of **inhibiting** immune response in a mammal, wherein the method comprises administering to the mammal an amount of at least one xanthine. . .
R.sup.1 or R.sup.3 being as defined above, and R.sup.2 is a C.sub.1 -C.sub.4 alkyl group;
wherein said amount is effective in **inhibiting** immune response by **inhibiting** the activity of IL-1, TNF, or other **leukocyte** derived cytokines on mononuclear phagocytes.

CLAIMS:

CLMS(11)

11. A method of **inhibiting** immune response in a mammal, wherein the method comprises administering to the mammal an amount of at least one 7-(oxoalkyl). . .
R.sup.1 or R.sup.3 being as defined above, and R.sup.2 is a C.sub.1 -C.sub.4 alkyl group;

wherein said amount is effective in **inhibiting** immune response by **inhibiting** the activity of IL-1, TNF, or other **leukocyte** derived cytokines on monocytes.

CLAIMS:

CLMS(12)

12. A method of **inhibiting** immune response in a mammal, wherein the method comprises administering to the mammal an amount of at least one xanthine. . .
R.sup.1 or R.sup.3 being as defined above, and R.sup.2 is a C.sub.1 -C.sub.4 alkyl group;
wherein said amount is effective in **inhibiting** immune response by **inhibiting** the activity of IL-1, TNF, or other **leukocyte** derived cytokines on macrophages.

CLAIMS:

CLMS(13)

13. A method of **inhibiting** immune response in a mammal, wherein the method comprises administering to the mammal an amount of at least one xanthine. . .
R.sup.1 or R.sup.3 being as defined above, and R.sup.2 is a C.sub.1 -C.sub.4 alkyl group;
wherein said amount is effective in **inhibiting** immune response by **inhibiting** the activity of IL-1, TNF, or other **leukocyte** derived cytokines on lymphocytes.

CLAIMS:

CLMS(16)

16. A method of **inhibiting** immune response in a mammal, wherein the method comprises administering to the mammal an amount of at least one xanthine. . .
oxygen atoms;
(e) C.sub.3 -C.sub.11 oxoalkyl group;
and in addition R.sub.1 and R.sub.2 can be cyclohexyl;
wherein said amount is effective in **inhibiting** immune response by **inhibiting** the activity of IL-1, TNF, or other **leukocyte** derived cytokines on polymorphonuclear **leukocytes**.

CLAIMS:

CLMS(17)

17. A method of **inhibiting** immune response in a mammal, wherein the method comprises administering to the mammal an amount of at least one xanthine. . .
oxygen atoms;
(e) C.sub.3 -C.sub.11 oxoalkyl group;
and in addition R.sub.1 and R.sub.2 can be cyclohexyl;
wherein said amount is effective in **inhibiting** immune response by **inhibiting** the activity of IL-1, TNF, or other **leukocyte** derived cytokines on neutrophils.

CLAIMS:

CLMS(18)

18. A method of **inhibiting** immune response in a mammal, wherein the method comprises administering to the mammal an amount of at least one xanthine. . .

chain may be interrupted by up to 2 oxygen atoms;
(e) C.sub.3 -C.sub.11 oxoalkyl group;
wherein said amount is effective in **inhibiting** immune response by **inhibiting** the activity of IL-1, TNF, or other **leukocyte** derived cytokines on mononuclear phagocytes.

CLAIMS:

CLMS(19)

19. A method of **inhibiting** immune response in a mammal, wherein the method comprises administering to the mammal an amount of at least one 7-(oxoalkyl). . .
oxygen atoms;
(e) C.sub.3 -C.sub.11 oxoalkyl group; , ,
and in addition R.sub.1 and R.sub.2 can be cyclohexyl;
wherein said amount is effective in **inhibiting** immune response by **inhibiting** the activity of IL-1, TNF, or other **leukocyte** derived cytokines on monocytes.

CLAIMS:

CLMS(20)

20. A method of **inhibiting** immune response in a mammal, wherein the method comprises administering to the mammal an amount of at least one xanthine. . .
oxygen atoms;
(e) C.sub.3 -C.sub.11 oxoalkyl group;
and in addition R.sub.1 and R.sub.2 can be cyclohexyl;
wherein said amount is effective in **inhibiting** immune response by **inhibiting** the activity of IL-1, TNF, or other **leukocyte** derived cytokines on macrophages.

CLAIMS:

CLMS(21)

21. A method of **inhibiting** immune response in a mammal, wherein the method comprises administering to the mammal an amount of at least one xanthine. . .
oxygen atoms;
(e) C.sub.3 -C.sub.11 oxoalkyl group;
and in addition R.sub.1 and R.sub.2 can be cyclohexyl;
wherein said amount is effective in **inhibiting** immune response by **inhibiting** the activity of IL-1, TNF, or other **leukocyte** derived cytokines on lymphocytes.

CLAIMS:

CLMS(26)

26. A method of **inhibiting** immune response in a mammal, wherein the method comprises administering to the mammal an amount of at least one xanthine. . .
or C.sub.1 -C.sub.9 branched chain hydroxyalkyl;
and in addition R.sub.1 and R.sub.2 can be cyclohexyl;
wherein said amount is effective in **inhibiting** immune response by **inhibiting** the activity of IL-1, TNF, or other **leukocyte** derived cytokines on polymorphonuclear **leukocytes**.

CLAIMS:

CLMS(27)

27. A method of **inhibiting** immune response in a mammal, wherein the method comprises administering to the mammal an amount of at least one xanthine. . .
or C.sub.1 -C.sub.9 branched chain hydroxyalkyl;
and in addition R.sub.1 and R.sub.2 can be cyclohexyl;
wherein said amount is effective in **inhibiting** immune response by **inhibiting** the activity of IL-1, TNF, or other **leukocyte** derived cytokines on neutrophils.

CLAIMS:

CLMS(28)

28. A method of **inhibiting** immune response in a mammal, wherein the method comprises administering to the mammal an amount of at least one xanthine. . .
or C.sub.1 -C.sub.9 branched chain hydroxyalkyl;
and in addition R.sub.1 and R.sub.2 can be cyclohexyl;
wherein said amount is effective in **inhibiting** immune response by **inhibiting** the activity of IL-1, TNF, or other **leukocyte** derived cytokines on mononuclear phagocytes.

CLAIMS:

CLMS(29)

29. A method of **inhibiting** immune response in a mammal, wherein the method comprises administering to the mammal an amount of at least one 7-(oxoalkyl). . .
C.sub.1 -C.sub.9 branched chain hydroxyalkyl;
and in addition R.sub.1 and R.sub.2 can be cyclohexyl;
wherein said amount is effective in **inhibiting** immune response by **inhibiting** the activity of IL-1, TNF, or other **leukocyte** derived cytokines on monocytes.

CLAIMS:

CLMS(30)

30. A method of **inhibiting** immune response in a mammal, wherein the method comprises administering to the mammal an amount of at least one xanthine. . .
or C.sub.1 -C.sub.9 branched chain hydroxyalkyl;
and in addition R.sub.1 and R.sub.2 can be cyclohexyl;
wherein said amount is effective in **inhibiting** immune response by **inhibiting** the activity of IL-1, TNF, or other **leukocyte** derived cytokines on macrophages.

CLAIMS:

CLMS(31)

31. A method of **inhibiting** immune response in a mammal, wherein the method comprises administering to the mammal an amount of at least one xanthine. . .
or C.sub.1 -C.sub.9 branched chain hydroxyalkyl;
and in addition R.sub.1 and R.sub.2 can be cyclohexyl;
wherein said amount is effective in **inhibiting** immune response by **inhibiting** the activity of IL-1, TNF, or other **leukocyte** derived cytokines on lymphocytes.

US PAT NO: 5,196,430 [IMAGE AVAILABLE] L6: 23 of 32
TITLE: Method of **inhibiting** the activity of **leukocyte** derived cytokines

ABSTRACT:
A family of compounds effective in **inhibiting** interleukin-1 (IL-1) activity, tumor necrosis factor (TNF) activity, and the activity of other **leukocyte** derived cytokines is comprised of 7-(oxoalkyl) 1,3-dialkyl xanthines of the formula ##STR1## in which R.sub.1 and R.sub.2 are the same. . . . carbon atoms which can be substituted by a methyl group. Another family of effective compounds is identified as ##STR2## The **inhibition** of IL-1, TNF, and other cytokines in mammals is implicated in alleviation of a wide variety of disease conditions.

SUMMARY:

BSUM(2)

This invention relates to the **inhibition** of activity of **leukocyte** derived cytokines, such as interleukin-1 and tumor necrosis factor, in humans and mammals. More specifically, this invention provides a method of **inhibiting** the activity of cytokines to arrest or alleviate certain disease and inflammatory states.

SUMMARY:

BSUM(3)

Interleukin-1 . . . wide variety of cells and tissues, both in vitro and in vivo. Research has demonstrated that IL-1, TNF, and other **leukocyte** derived cytokines are important, and even critical, mediators in a wide variety of inflammatory states and diseases. The **inhibition** of IL-1, TNF, and other **leukocyte** derived cytokines is of benefit in controlling, reducing, and alleviating many of these conditions.

SUMMARY:

BSUM(4)

Detection and **inhibition** of IL-1, TNF, and other **leukocyte** derived cytokines can be relatively easily documented through in vitro analysis of polymorphonuclear neutrophil behavior. Among other activities attributed to IL-1 and other **leukocyte** derived cytokines is the promotion of **leukocyte** adherence and the **inhibition** of neutrophil chemotaxis, both directly contributing to disease and inflammation syndromes.

SUMMARY:

BSUM(5)

Despite the desirability of **inhibiting** the activity of IL-1 and TNF and the activity of other **leukocyte** derived cytokines and the ease with which **inhibition** can be detected in vitro, there exists a need in the art for **inhibitors** of IL-1, TNF, and other cytokines, wherein the **inhibitors** are acceptable for in vivo administration.

SUMMARY:

BSUM(7)

This . . . class of compounds that can be successfully employed in alleviating conditions caused by, or mediated by, IL-1, TNF, and other **leukocyte** derived cytokines. The compounds exhibit marked **inhibition** of cytokine activity, even at low concentrations of the mediators as demonstrated through in vitro tests.

SUMMARY:

BSUM(8)

More particularly, this invention provides a method of **inhibiting** the activity of IL-1, TNF, and other **leukocyte** derived cytokines in a mammal comprising administering thereto at least one 7-(oxoalkyl) 1,3-dialkyl xanthine of the formula (I) ##STR3## in. . .

SUMMARY:

BSUM(9)

A . . . 4 carbon atoms. The xanthine of formula (I) or formula (II) is employed in an amount that is effective in **inhibiting** the activity of IL-1, TNF, and other **leukocyte** derived cytokines in the mammal.

SUMMARY:

BSUM(10)

Exemplary within the general formula (II), and established as an effective IL-1 **inhibitor**, is the well known and commercially available pharmaceutical pentoxifylline. Although this compound has been used for some time as a pharmaceutical (clinical trials in 1971) it has not been reported effective as an IL-1 **inhibitor**. It has been demonstrated in promoting directed migration of **leukocytes**.

DETDESC:

DETD(2)

Inhibition of the activity of IL-1, TNF, and other **leukocyte** derived cytokines can be achieved by the administration of xanthines of formula (I) or formula (II) to a mammal.

DETDESC:

DETD(4)

The term "cytokine" as used herein means a secretory product of a **leukocyte**, and in particular a non-antibody protein released by a **leukocyte** on contact with antigen and which acts as an intercellular mediator of immune response. Examples of cytokines that are within the scope of this invention are chemotactic factors, factors promoting replication of lymphocytes, factors **inhibiting** replication of lymphocytes, factors affecting macrophage adherence, factors affecting enzyme secretion by macrophages, and factors that mediate secretion of oxidizing. . .

DETDESC:

DETD(6)

A compound that has been found to be particularly effective for **inhibiting** the effects of IL-1 and other **leukocyte** derived cytokines on polymorphonuclear **leukocytes** and monocytes is 1,3-dibutyl 7-(2-oxopropyl) xanthine. This compound, which is also referred to herein in abbreviated form as "DBOPX", has the following formula: ##STR8## The ability of compound (III) to **inhibit** the effects of IL-1 and other **leukocyte** derived cytokines on polymorphonuclear **leukocyte** and monocyte adherence, cell chemotaxis, respiratory (metabolic) burst, and cell degranulation has been demonstrated and is described hereinafter.

DETDESC:

DETD(22)

Leukocyte response to an acute inflammatory stimulus involves a complex series of events, including adherence to endothelium near the stimulus. **Inhibition** of **leukocyte** adherence can be expected to reduce the degree of inflammation seen in conditions, such a septic shock and adult respiratory distress syndrome. It has been found that the 7-(oxoalkyl) 1,3-dialkyl xanthines employed in this invention effectively **block** adherence of polymorphonuclear **leukocytes**.

DETDESC:

DETD(24)

FIG. . . . However, when DBOPX was included in the assay at concentrations above about 0.1 .mu.g/ml, PMN adherence to the nylon was **inhibited** as evidenced by a decline in percent adherence. At a DBOPX concentration of 10 .mu.g/ml, the percent PMN adherence declined. . . incubated with conditioned medium was 99.7%. Thus, the compounds employed in the process of this invention are particularly effective in **blocking** adherence of **leukocytes** and thereby aiding in reducing the degree of inflammation.

DETDESC:

DETD(35)

Referring to FIG. 7, lysozyme released by PMN primed with LPS-stimulated mononuclear **leukocyte** conditioned medium (containing inflammatory cytokines) and stimulated with FMLP was about 2.1 .mu.g/ml in the absence of DBOPX. When DBOPX. . . .mu.g/ml. At a DBOPX concentration of 100 .mu.g/ml, the lysozyme release was only about 1.04 .mu.g/ml. The probability that DBOPX **inhibited** lysozyme release from PMN primed with conditioned medium and stimulated with FMLP was 95%.

DETDESC:

DETD(37)

In summary, the compounds of formula (I) employed in the process of this invention are capable of modulating the effects of **leukocyte** derived cytokines, such as interleukin-1 and tumor necrosis factor, on phagocytes, such as polymorphonuclear **leukocytes**. The compounds are capable of substantially aiding chemotaxis. In addition, the compounds can **block** adherence of cells. The compounds can decrease oxidative damage to host tissues by phagocytes as evidenced by modulation of respiratory burst in stimulated polymorphonuclear **leukocytes**. Finally, the compounds can modulate the effects of cytokines on degranulation in stimulated phagocytes. The demonstrated **inhibition** of IL-1, TNF, and other cytokines by these compounds is suggestive of clinical effectiveness in at least the following areas. . .

DETDESC:

DETD(38)

Because IL-1, TNF, and other **leukocyte** derived cytokines have been implicated in such a wide variety of mammalian conditions, this invention has a similarly broad scope of application. Among the conditions that can be treated or alleviated by the **inhibition** of IL-1, TNF, and other **leukocyte** derived cytokines are: sepsis, septic shock, endotoxic shock, gram negative sepsis, toxic shock syndrome, adult respiratory distress, fever and myalgias. . .

DETDESC:

DETD(42)

Representative viruses are: Rhinovirus; Parainfluenza; Enterovirus; Influenza; Smallpox and vaccinia; **Herpes** simplex; Measles; Rubella; **Arbovirus** (Western, Eastern and Venezuelan equine **encephalitis**, and California **encephalitis**); Rabies; Colorado tick fever; Yellow fever; Dengue; Hepatitis Virus B (HB Ag); Hepatitis Virus A (HAV); and Human Immunodeficiency Virus. . .

DETDESC:

DETD(46)

In addition, **inhibition** of IL-1, TNF, and other **leukocyte** derived cytokines will enhance phagocyte activity in stored blood and blood products.

DETDESC:

DETD(117)

To demonstrate the effectiveness of the claimed invention, a compound of the general formula (I) was tested to demonstrate **inhibition** of the activity of both in vitro-generated human IL-1 and other **leukocyte** derived cytokines, and purified human IL-1. Though a variety of compounds within the general formula (I) are effective in **inhibiting** the activites of IL-1 and other **leukocyte** derived cytokines, they will be exemplified with regard to 1,3-dibutyl 7-(2-oxopropyl)xanthine (DBPOX) as a particularly preferred form of the invention.

DETDESC:

DETD(130)

DBOPX increased chemotaxis **inhibited** by IL-1, TNF, or LPS stimulated mononuclear **leukocyte** conditioned medium as shown in FIGS. 1, 2 and 3.

CLAIMS:

CLMS(38)

38. A method of **inhibiting** immune response in a mammal, wherein the method comprises administering to the mammal an amount of at least one 7-(oxoalkyl). . .
with up to 4 carbon atoms, which can be substituted by a methyl group; and
wherein said amount is effective in **inhibiting** immune response by **inhibiting** the activity of IL-1, TNF, or other **leukocyte** derived cytokines on polymorphonuclear **leukocytes**.

CLAIMS:

CLMS(39)

39. A method of **inhibiting** immune response in a mammal, wherein the method comprises administering to the mammal an amount of at least one 7-(oxoalkyl). . .
with up to 4 carbon atoms, which can be substituted by a methyl group; and
wherein said amount is effective in **inhibiting** immune response by **inhibiting** the activity of IL-1, TNF, or other **leukocyte** derived cytokines on neutrophils.

CLAIMS:

CLMS(40)

40. A method of **inhibiting** immune response in a mammal, wherein the method comprises administering to the mammal an amount of at least one 7-(oxoalkyl). . .
with up to 4 carbon atoms, which can be substituted by a methyl group; and
wherein said amount is effective in **inhibiting** immune response by **inhibiting** the activity of IL-1, TNF, or other **leukocyte** derived cytokines on mononuclear phagocytes.

CLAIMS:

CLMS(41)

41. A method of **inhibiting** immune response in a mammal, wherein the method comprises administering to the mammal an amount of at least one 7-(oxoalkyl). . .
with up to 4 carbon atoms, which can be substituted by a methyl group; and
wherein said amount is effective in **inhibiting** immune response by **inhibiting** the activity of IL-1, TNF, or other **leukocyte** derived cytokines on monocytes.

CLAIMS:

CLMS(42)

42. A method of **inhibiting** immune response in a mammal, wherein the method comprises administering to the mammal an amount of at least one 7-(oxoalkyl). . .
with up to 4 carbon atoms, which can be substituted by a methyl group; and
wherein said amount is effective in **inhibiting** immune response by **inhibiting** the activity of IL-1, TNF, or other **leukocyte** derived cytokines on macrophages.

CLAIMS:

CLMS(43)

43. A method of **inhibiting** immune response in a mammal, wherein the method comprises administering to the mammal an amount of at least one 7-(oxoalkyl). . .
with up to 4 carbon atoms, which can be substituted by a methyl group; and
wherein said amount is effective in **inhibiting** immune response by **inhibiting** the activity of IL-1, TNF, or other **leukocyte** derived cytokines on lymphocytes.

CLAIMS:

CLMS(48)

48. A method of **inhibiting** cellular attack by human immunodeficiency virus (HIV) and physical injury of cells in a human, wherein the method comprises administering. . .
radical with up to 4 carbon atoms, which can be substituted by a methyl group;
wherein said amount is sufficient to **inhibit** the activity of human **leukocyte**-derived cytokines in the human and thereby **inhibit** said cellular attack and said physical injury of the cells.

US PAT NO: 5,196,429 [IMAGE AVAILABLE] L6: 24 of 32
TITLE: Method of **inhibiting** the activity of **leukocyte** derived cytokines

ABSTRACT:
A family of compounds effective in **inhibiting** interleukin-1 (IL-1) activity, tumor necrosis factor (TNF) activity, and the activity of other **leukocyte** derived cytokines is comprised of 7-(oxoalkyl) 1,3-dialkyl xanthines of the formula ##STR1## in which R.sub.1 and R.sub.2 are the same. . . . carbon atoms which can be substituted by a methyl group. Another family of effective compounds is identified as ##STR2## The **inhibition** of IL-1, TNF, and other cytokines in mammals is implicated in alleviation of a wide variety of disease conditions.

SUMMARY:

BSUM(2)

The invention relates to the **inhibition** of activity of **leukocyte** derived cytokines, such as interleukin-1 and tumor necrosis factor, in humans and mammals. More specifically, this invention provides a method of **inhibiting** the activity of cytokines to arrest or alleviate certain disease and inflammatory states.

SUMMARY:

BSUM(3)

Interleukin-1 . . . wide variety of cells and tissues, both in vitro and in vivo. Research has demonstrated that IL-1, TNF, and other **leukocyte** derived cytokines are important, and even critical, mediators in a wide variety of inflammatory states and diseases. The **inhibition** of IL-1, TNF, and other **leukocyte** derived cytokines is of benefit in controlling, reducing, and alleviating many of these conditions.

SUMMARY:

BSUM(4)

Detection and **inhibition** of IL-1, TNF, and other **leukocyte** derived cytokines can be relatively easily documented through in vitro analysis of polymorphonuclear neutrophil behavior. Among other activities attributed to IL-1 and other **leukocyte** derived cytokines is the promotion of **leukocyte** adherence and the **inhibition** of neutrophil chemotaxis, both directly contributing to disease and inflammation syndromes.

SUMMARY:

BSUM(5)

Despite the desirability of **inhibiting** the activity of IL-1 and TNF and the activity of other **leukocyte** derived cytokines and the ease with which **inhibition** can be detected in vitro, there exists a need in the art for **inhibitors** of IL-1, TNF, and other cytokines, wherein the **inhibitors** are acceptable for in vivo administration.

SUMMARY:

BSUM(7)

This . . . class of compounds that can be successfully employed in alleviating conditions caused by, or mediated by, IL-1, TNF, and other

leukocyte derived cytokines. The compounds exhibit marked **inhibition** of cytokine activity, even at low concentrations of the mediators as demonstrated through in vitro tests.

SUMMARY:

BSUM(8)

More particularly, this invention provides a method in **inhibiting** the activity of IL-1, TNF, and other **leukocyte** derived cytokines in a mammal comprising administering thereto at least one 7-(oxoalkyl) 1,3-dialkyl xanthine of the formula (I) ##STR3## in. . .

SUMMARY:

BSUM(10)

a . . . 4 carbon atoms. The xanthine of formula (I) or formula (II) is employed in an amount that is effective in **inhibiting** the activity of IL-1, TNF, and other **leukocyte** derived cytokines in the mammal.

SUMMARY:

BSUM(11)

Exemplary within the general formula (II), and established as an effective IL-1 **inhibitor**, is the well known and commercially available pharmaceutical pentoxifylline. Although this compound has been used for some time as a pharmaceutical (clinical trials in 1971) it has not been reported effective as an IL-1 **inhibitor**. It has been demonstrated in promoting directed migration of **leukocytes**.

DETDESC:

DETD(2)

Inhibition of the activity of IL-1, TNF, and other **leukocyte** derived cytokines can be achieved by the administration of xanthines of formula (I) or formula (II) to a mammal.

DETDESC:

DETD(4)

The term "cytokine" as used herein means a secretory product of a **leukocyte**, and in particular a non-antibody protein released by a **leukocyte** on contact with antigen and which acts as an intercellular mediator of immune response. Examples of cytokines that are within the scope of this invention are chemotactic factors, factors promoting replication of lymphocytes, factors **inhibiting** replication of lymphocytes, factors affecting macrophage adherence, factors affecting enzyme secretion by macrophages, and factors that mediate secretion of oxidizing. . .

DETDESC:

DETD(6)

A compound that has been found to be particularly effective for **inhibiting** the effects of IL-1 and other **leukocyte** derived cytokines on polymorphonuclear **leukocytes** and monocytes is 1,3-dibutyl 7-(2-oxopropyl) xanthine. This compound, which is also referred to herein in abbreviated form as "DBOPX", has the following formula: ##STR8## The ability of compound (III) to **inhibit** the effects of IL-1 and other **leukocyte** derived cytokines on

polymorphonuclear **leukocyte** and monocyte adherence, cell chemotaxis, respiratory (metabolic) burst, and cell degranulation has been demonstrated and is described hereinafter.

DETDESC:

DETD(22)

Leukocyte response to an acute inflammatory stimulus involves a complex series of events, including adherence to endothelium near the stimulus. **Inhibition** of **leukocyte** adherence can be expected to reduce the degree of inflammation seen in conditions, such as septic shock and adult respiratory distress syndrome. It has been found that the 7-(oxoalkyl) 1,3-dialkyl xanthines employed in this invention effectively **block** adherence of polymorphonuclear **leukocytes**.

DETDESC:

DETD(24)

FIG. . . . However, when DBOPX was included in the assay at concentrations above about 0.1 .mu.g/ml, PMN adherence to the nylon was **inhibited** as evidenced by a decline in percent adherence. AT a DBOPX concentration of 10 .mu.g/ml, the percent PMN adherence declined. . . incubated with conditioned medium was 99.7%. Thus, the compounds employed in the process of this invention are particularly effective in **blocking** adherence of **leukocytes** and thereby aiding in reducing the degree of inflammation.

DETDESC:

DETD(35)

Referring to FIG. 7, lysozyme released by PMN primed with LPS-stimulated mononuclear **leukocyte** conditioned medium (containing inflammatory cytokines) and stimulated with FMLP was about 2.1 .mu.g/ml in the absence of DBOPX. When DBOPX. . . .mu.g/ml. At a DBOPX concentration of 100 .mu.g/ml, the lysozyme release was only about 1.04 .mu.g/ml. The probability that DBOPX **inhibited** lysozyme release from PMN primed with conditioned medium and stimulated with FMLP was 95%.

DETDESC:

DETD(37)

In summary, the compounds of formula (I) employed in the process of this invention are capable of modulating the effects of **leukocyte** derived cytokines, such as interleukin-1 and tumor necrosis factor, on phagocytes, such as polymorphonuclear **leukocytes**. The compounds are capable of substantially aiding chemotaxis. In addition, the compounds can **block** adherence of cells. The compounds can decrease oxidative damage to host tissues by phagocytes as evidenced by modulation of respiratory burst in stimulated polymorphonuclear **leukocytes**. Finally, the compounds can modulate the effects of cytokines on degranulation is stimulated phagocytes. The demonstrated **inhibition** of IL-1, TNF, and other cytokines by these compounds is suggestive of clinical effectiveness is at least the following areas. . .

DETDESC:

DETD(38)

Because IL-1, TNF, and other **leukocyte** derived cytokines have been implicated in such a wide variety of mammalian conditions, this invention has a similarly broad scope of application. Among the conditions that can

be treated or alleviated by the **inhibition** of IL-1, TNF, and other **leukocyte** derived cytokines are: sepsis, septic shock, endotoxic shock, gram negative sepsis, toxic shock syndrome, adult respiratory distress, fever and myalgias. . .

DETDESC:

DETD(42)

Representative viruses are: Rhinovirus; Parainfluenza; Enterovirus; Influenza; Smallpox and vaccinia; **Herpes** simplex; Measles; Rubella; **Arbovirus** (Western, Eastern and Venezuelan equine **encephalitis**, and California **encephalitis**); Rabies; Colorado tick fever; Yellow fever; Dengue; Hepatitis Virus B (HB Ag); Hepatitis Virus A (HAV); and Human Immunodeficiency Virus. . . .

DETDESC:

DETD(46)

In addition, **inhibition** of IL-1, TNF, and other **leukocyte** derived cytokines will enhance phagocyte activity in stored blood and blood products.

DETDESC:

DETD(117)

To demonstrate the effectiveness of the claimed invention, a compound of the general formula (I) was tested to demonstrate **inhibition** of the activity of both in vitro-generated human IL-1 and other **leukocyte** derived cytokines, and purified human IL-1. Though a variety of compounds within the general formula (I) are effective in **inhibiting** the activities of IL-1 and other **leukocyte** derived cytokines, they will be exemplified with regard to 1,3-dibutyl 7-(2-oxopropyl)xanthine (DBPOX) as a particularly preferred form of the invention.

DETDESC:

DETD(130)

DBOPX increased chemotaxis **inhibited** by IL-1, TNF, or LPS stimulated mononuclear **leukocyte** conditioned medium as shown in FIGS. 1, 2, and 3.

CLAIMS:

CLMS(2)

2. A method of **inhibiting** cellular attack by human immunodeficiency virus (HIV) and physical injury of cells in a human, wherein the method comprises administering. . .
R.sup.1 or R.sup.3 being as defined above, and R.sup.2 is a C.sub.1 -C.sub.4 alkyl group;
wherein said amount is sufficient to **inhibit** the activity of human **leukocyte**-derived cytokines in the human and thereby **inhibit** said cellular attack and said physical injury of the cells.

US PAT NO: 5,096,906 [IMAGE AVAILABLE] L6: 28 of 32
TITLE: Method of **inhibiting** the activity of **leukocyte** derived cytokines

ABSTRACT:
A family of compounds effective in **inhibiting** interleukin-1 (IL-1) activity, tumor necrosis factor (TNF) activity, and the activity of other

leukocyte derived cytokines is comprised of 7-(oxoalkyl) 1,3-dialkyl xanthines of the formula ##STR1## in which R.sub.1 and R.sub.2 are the same. . . . carbon atoms which can be substituted by a methyl group. Another family of effective compounds is identified as ##STR2## The **inhibition** of IL-1, TNF, and other cytokines in mammals is implicated in alleviation of a wide variety of disease conditions.

SUMMARY:

BSUM(2)

This invention relates to the **inhibition** of activity of **leukocyte** derived cytokines, such as interleukin-1 and tumor necrosis factor, in humans and mammals. More specifically, this invention provides a method of **inhibiting** the activity of cytokines to arrest or alleviate certain disease and inflammatory states.

SUMMARY:

BSUM(3)

Interleukin-1 . . . wide variety of cells and tissues, both in vitro and in vivo. Research has demonstrated that IL-1, TNF, and other **leukocyte** derived cytokines are important, and even critical, mediators in a wide variety of inflammatory states and diseases. The **inhibition** of IL-1, TNF, and other **leukocyte** derived cytokines is of benefit in controlling, reducing, and alleviating many of these conditions.

SUMMARY:

BSUM(4)

Detection and **inhibition** of IL-1, TNF, and other **leukocyte** derived cytokines can be relatively easily documented through in vitro analysis of polymorphonuclear neutrophil behavior. Among other activities attributed to IL-1and other **leukocyte** derived cytokines is the promotion of leukoctye adherence and the **inhibition** of neutrophil chemotaxis, both directly contributing to disease and inflammation syndromes.

SUMMARY:

BSUM(5)

Despite the desirability of **inhibiting** the activity of IL-1 and TNF and the activity of other **leukocyte** derived cytokines and the ease with which **inhibition** can be detected in vitro, there exists a need in the art for **inhibitors** of IL-1, TNF, and other cytokines, wherein the **inhibitors** are acceptable for in vivo administration.

SUMMARY:

BSUM(7)

This . . . class of compounds that can be successfully employed in alleviating conditions caused by, or mediated by, IL-1, TNF, and other **leukocyte** derived cytokines. The compounds exhibit marked **inhibition** of cytokine activity, even at low concentrations of the mediators as demonstrated through in vitro tests.

SUMMARY:

BSUM(8)

More particularly, this invention provides a method of **inhibiting** the activity of IL-1, TNF, and other **leukocyte** derived cytokines in a mammal comprising administering thereto at least one 7-(oxoalkyl) 1,3-dialkyl xanthine of the formula (I) ##STR3## in. . .

SUMMARY:

BSUM(10)

Exemplary within the general formula (II), and established as an effective IL-1 **inhibitor**, is the well known and commercially available pharmaceutical pentoxifylline. Although this compound has been used for some time as a pharmaceutical (clinical trials in 1971) it has not been reported effective as an IL-1 **inhibitor**. It has been demonstrated in promoting directed migration of **leukocytes**.

DETDESC:

DETD(2)

Inhibition of the activity of IL-1, TNF, and other **leukocyte** derived cytokines can be achieved by the administration of xanthines of formula (I) or formula (II) to a mammal.

DETDESC:

DETD(4)

The term "cytokine" as used herein means a secretory product of a **leukocyte**, and in particular a non-antibody protein released by a **leukocyte** on contact with antigen and which acts as an intercellular mediator of immune response. Examples of cytokines that are within the scope of this invention are chemotactic factors, factors promoting replication of lymphocytes, factors **inhibiting** replication of lymphocytes, factors affecting macrophage adherence, factors affecting enzyme secretion by macrophages, and factors that mediate secretion of oxidizing. . .

DETDESC:

DETD(6)

A compound that has been found to be particularly effective for **inhibiting** the effects of IL-1 and other **leukocyte** derived cytokines on polymorphonuclear **leukocytes** and monocytes is 1,3-dibutyl 7-(2-oxopropyl) xanthine. This compound, which is also referred to herein in abbreviated form as "DBOPX", has the following formula: ##STR8## The ability of compound (III) to **inhibit** the effects of IL-1 and other **leukocyte** derived cytokines on polymorphonuclear **leukocyte** and monocyte adherence, cell chemotaxis, respiratory (metabolic) burst, and cell degranulation has been demonstrated and is described hereinafter.

DETDESC:

DETD(22)

Leukocyte response to an acute inflammatory stimulus involves a complex series of events, including adherence to endothelium near the stimulus. **Inhibition** of **leukocyte** adherence can be expected to reduce the degree of inflammation seen in conditions, such a septic shock and adult respiratory distress syndrome. It has been found that the 7-(oxoalkyl) 1,3-dialkyl xanthines employed in this invention effectively **block** adherence of polymorphonuclear **leukocytes**.

DETDESC:

DETD(24)

FIG. . . . However, when DBOPX was included in the assay at concentrations above about 0.1 .mu.g/ml, PMN adherence to the nylon was **inhibited** as evidenced by a decline in percent adherence. At a DBOPX concentration of 10 .mu.g/ml, the percent PMN adherence declined. . . incubated with conditioned medium was 99.7%. Thus, the compounds employed in the process of this invention are particularly effective in **blocking** adherence of **leukocytes** and thereby aiding in reducing the degree of inflammation.

DETDESC:

DETD(35)

Referring to FIG. 7, lysozyme released by PMN primed with LPS-stimulated mononuclear **leukocyte** conditioned medium (containing inflammatory cytokines) and stimulated with FMLP was about 2.1 .mu.g/ml in the absence of DBOPX. When DBOPX. . . .mu.g/ml. At a DBOPX concentration of 100 .mu.g/ml, the lysozyme release was only about 1.04 .mu./ml. The probability that DBOPX **inhibited** lysozyme release from PMN primed with conditioned medium and stimulated with FMLP was 95%.

DETDESC:

DETD(37)

In summary, the compounds of formula (I) employed in the process of this invention are capable of modulating the effects of **leukocyte** derived cytokines, such as interleukin-1 and tumor necrosis factor, on phagocytes, such as polymorphonuclear **leukocytes**. The compounds are capable of substantially aiding chemotaxis. In addition, the compounds can **block** adherence of cells. The compounds can decrease oxidative damage to host tissues by phagocytes as evidenced by modulation of respiratory burst in stimulated polymorphonuclear **leukocytes**. Finally the compounds can modulate the effects of cytokines on degranulation in stimulated phagocytes. The demonstrated **inhibition** of IL-1, TNF, and other cytokines by these compounds is suggestive of clinical effectiveness in at least the following areas. . .

DETDESC:

DETD(38)

Because IL-1, TNF, and other **leukocyte** derived cytokines have been implicated in such a wide variety of mammalian conditions, this invention has a similarly broad scope of application. Among the conditions that can be treated or alleviated by the **inhibition** of IL-1, TNF, and other **leukocyte** derived cytokines are: sepsis, septic shock, endotoxic shock, gram negative sepsis, toxic shock syndrome, adult respiratory distress, fever and myalgias. . .

DETDESC:

DETD(42)

Representative viruses are: Rhinovirus; Parainfluenza; Enterovirus; Influenza; Smallpox and vacinnia; **Herpes** simplex; Measles; Rubella; **Arbovirus** (Western, Eastern and Venezuelan equine **encephalitis**, and California **encephalitis**); Babies; Colorado tick fever; Yellow fever; Dengue; Hepatitis Virus B (HB Ag); Hepatitis Virus A (HAV); and Human Immunodeficiency Virus. . .

DETDESC:

DETD(46)

In addition, **inhibition** of IL-1, TNF, and other **leukocyte** derived cytokines will enhance phagocyte activity in stored blood and blood products.

DETDESC:

DETD(116)

To demonstrate the effectiveness of the claimed invention, a compound of the general formula (I) was tested to demonstrate **inhibition** of the activity of both in vitro-generated human IL-1 and other **leukocyte** derived cytokines, and purified human IL-1. Though a variety of compounds within the general formula (I) are effective **inhibiting** the activities of IL-1 and other **leukocyte** derived cytokines, they will be exemplified with regard to 1,3-dibutyl 7(2-oxopropyl)xanthine (DBPOX) as a particularly preferred form of the invention.

DETDESC:

DETD(129)

DBOPX increased chemotaxis **inhibited** by IL-1, TNF, or LPS stimulated mononuclear **leukocyte** conditioned medium as shown in FIGS. 1, 2 and 3.

CLAIMS:

CLMS(1)

What is claimed is:

1. A method of treating a human to **inhibit** tissue injury accompanying inflammation resulting from **leukocyte** activity induced by cytokines produced in response to an inflammatory stimulus in the human, wherein the method comprises administering to. . .
is an alkyl group C.sub.1 -C.sub.4 ;
wherein said compound is administered to said human in an amount sufficient to **inhibit** activity of human interleukin-1, human tumor necrosis factor, or the activity of other human **leukocyte**-derived human cytokines on polymorphonuclear **leukocytes** or monocytes in said human to thereby **inhibit** said tissue injury.

CLAIMS:

CLMS(3)

3. A method of treating a human to **inhibit** tissue injury accompanying inflammation resulting from **leukocyte** activity induced by cytokines produced in response to an inflammatory stimulus in the human, wherein the method comprises administering to. . .
human in an amount sufficient to modulate the inflammatory effect of human interleukin-1, human tumor necrosis factor, or other human **leukocyte**-derived cytokines on polymorphonuclear **leukocyte** or monocytes by counteracting the **inhibitory** effect on cell movement in said human.

CLAIMS:

CLMS(5)

5. A method of treating a human to **inhibit** tissue injury

accompanying inflammation resulting from **leukocyte** activity induced by cytokines produced in response to an inflammatory stimulus in the human, wherein the method comprises administering to. . .
is an alkyl group C.sub.1 -C.sub.4 ;
wherein said compound is administered to said human in an amount sufficient to **inhibit** the stimulatory effect of human interleukin-1, human tumor necrosis factor, or other human **leukocyte**-derived cytokines on adherence of polymorphonuclear **leukocytes** or monocytes in said human to thereby **inhibit** said tissue injury.

CLAIMS:

CLMS(7)

7. A method of treating a human to **inhibit** tissue injury accompanying inflammation resulting from **leukocyte** activity induced by cytokines produced in response to an inflammatory stimulus in the human, wherein the method comprises administering to. . .
is an alkyl group C.sub.1 -C.sub.4 ;
wherein said compound is administered to said human in an amount sufficient to **inhibit** stimulatory effect of human interleukin-1, human tumor necrosis factor, or other human **leukocyte**-derived human cytokines on oxidative burst of stimulated polymorphonuclear **leukocytes** in said human to thereby **inhibit** said tissue injury.

CLAIMS:

CLMS(9)

9. A method of treating a human to **inhibit** tissue injury accompanying inflammation resulting from **leukocyte** activity induced by cytokines produced in response to an inflammatory stimulus in the human, wherein the method comprises administering to. . .
is an alkyl group C.sub.1 -C.sub.4 ;
wherein said compound is administered to said human in an amount sufficient to **inhibit** the activity of human interleukin-1, human tumor necrosis factor, or other human **leukocyte**-derived human cytokine on degranulation of stimulated polymorphonuclear **leukocytes** in said human to thereby **inhibit** said tissue injury.

CLAIMS:

CLMS(11)

11. A method of treating a human to **inhibit** tissue injury accompanying inflammation resulting from **leukocyte** activity induced by cytokines produced in response to an inflammatory stimulus in the human, wherein the method comprises administering to. . .
is an alkyl group C.sub.1 -C.sub.4 ;
wherein said compound is administered to said human in an amount sufficient to **inhibit** the effect of human interleukin-1 or human tumor necrosis factor on oxidative burst or degranulation of stimulated neutrophils in said human to thereby **inhibit** said tissue injury.

CLAIMS:

CLMS(13)

13. . . .
is an alkyl group C.sub.1 -C.sub.4 ;
wherein said compound is administered to said human in an amount sufficient to **inhibit** activity of human interleukin-1, human tumor necrosis factor, or the activity of other human **leukocytes** or monocytes in said human to thereby **inhibit** said tissue injury.

US PAT NO: 4,965,271 [IMAGE AVAILABLE] L6: 29 of 32
TITLE: Method of **inhibiting** the activity of **leukocyte** derived cytokines

ABSTRACT:
A family of compounds effective in **inhibiting** interleukin-1 (IL-1) activity, tumor necrosis factor (TNF) activity, and the activity of other **leukocyte** derived cytokines is comprised of 7-(oxoalkyl) 1,3-dialkyl xanthines of the formula ##STR1## in which R.sub.1 and R.sub.2 are the same. . . . A represents a hydrocarbon radical with up to 4 carbon atoms which can be substituted by a methyl group. The **inhibition** of Il-1, TNF, and other cytokines in mammals is implicated in allerviation of a wide variety of disease conditions.

PARENT-CASE:

CROSS-REFERENCE . . .

This application is a continuation-in-part of copending application Ser. No. 947,905, filed Dec. 31, 1986, now abandoned for METHOD OF **INHIBITING** INTERLEUKIN-1 ACTIVITY AND THAT OF OTHER **LEUKOCYTE** DERIVED CYTOKINES, by Gerald L. Mandell, Gail W. Sullivan, and William J. Novick. The entire disclosure of the related, copending. . .

SUMMARY:

BSUM(2)

This invention relates to the **inhibition** of activity of **leukocyte** derived cytokines, such as interleukin-1 and tumor necrosis factor, in humans and mammals. More specifically, this invention provides a method of **inhibiting** the activity of cytokines to arrest or alleviate certain disease and inflammatory states.

SUMMARY:

BSUM(3)

Interleukin-1 . . . wide variety of cells and tissues, both in vitro and in vivo. Research has demonstrated that IL-1, TNF, and other **leukocyte** derived cytokines are important, and even critical, mediators in a wide variety of inflammatory states and diseases. The **inhibition** of IL-1, TNF, and other **leukocyte** derived cytokines is of benefit in controlling, reducing, and alleviating many of these conditions.

SUMMARY:

BSUM(4)

Detection on and **inhibition** of IL-1, TNF, and other **leukocyte** derived cytokines can be relatively easily documented through in vitro analysis of polymorphonuclear neutrophil behavior. Among other activities attributed to IL-1 and other **leukocyte** derived cytokines is the promotion of **leukocyte** adherence and the **inhibition** of neutrophil chemotaxis, both directly contributing to disease and inflammation syndromes.

SUMMARY:

BSUM(5)

Despite the desirability of **inhibiting** the activity of IL-1 and TNF and the activity of other **leukocyte** derived cytokines and the ease with which **inhibition** can be detected in vitro, there exists a need

in the art for **inhibitors** of IL-1, TNF, and other cytokines, wherein the **inhibitors** are acceptable for in vivo administration.

SUMMARY:

BSUM(7)

This . . . class of compounds that can be successfully employed in alleviating conditions caused by, or mediated by, IL-1, TNF, and other **leukocyte** derived cytokines. The compounds exhibit marked **inhibition** of cytokine activity, even at low concentrations of the mediators as demonstrated through in vitro tests.

SUMMARY:

BSUM(8)

More particularly, this invention provides a method of **inhibiting** the activity of IL-1, TNF, and other **leukocyte** derived cytokines in a mammal comprising administering thereto at least one 7-(oxoalkyl) 1,3-dialkyl xanthine of the formula ##STR2## in which

SUMMARY:

BSUM(10)

A . . . atoms which can be substituted by a methyl group. The xanthine is employed in an amount that is effective in **inhibiting** the activity of IL-1, TNF, and other **leukocyte** derived cytokines in the mammal.

DETDESC:

DETD(2)

Inhibition of the activity of IL-1, TNF, and other **leukocyte** derived cytokines can be achieved by the administration of 7-(oxoalkyl) 1,3-dialkyl xanthines to a mammal.

DETDESC:

DETD(4)

The term "cytokine" as used herein means a secretory product of a **leukocyte**, and in particular a non-antibody protein released by a **leukocyte** on contact with antigen and which acts as an intercellular mediator of immune response. Examples of cytokines that are within the scope of this invention are chemotactic factors, factors promoting replication of lymphocytes, factors **inhibiting** replication of lymphocytes, factors affecting macrophage adherence, factors affecting enzyme secretion by macrophages, and factors that mediate secretion of oxidizing. . .

DETDESC:

DETD(6)

A compound that has been found to be particularly effective for **inhibiting** the effects of IL-1 and other **leukocyte** derived cytokines on polymorphonuclear **leukocytes** and monocytes is 1,3-dibutyl 7-(2-oxopropyl) xanthine. This compound, which is also referred to herein in abbreviated form as "DBOPX", has the following formula: ##STR4## The ability of compound (II) to **inhibit** the effects of IL-1 and other **leukocyte** derived cytokines on polymorphonuclear **leukocyte** and monocyte adherence, cell chemotaxis, respiratory

(metabolic) burst, and cell degranulation has been demonstrated and is described hereinafter.

DETDESC:

DETD(18)

Leukocyte response to an acute inflammatory stimulus involves a complex series of events, including adherence to endothelium near the stimulus. **Inhibition** of **leukocyte** adherence can be expected to reduce the degree of inflammation seen in conditions, such a septic shock and adult respiratory distress syndrome. It has been found that the 7-(oxoalkyl) 1,3-dialkyl xanthines employed in this invention effectively **block** adherence of polymorphonuclear **leukocytes**.

DETDESC:

DETD(21)

FIG. . . . However, when DBOPX was included in the assay at concentrations above about 0.1 .mu.g/ml, PMN adherence to the nylon was **inhibited** as evidenced by a decline in percent adherence. At a DBOPX concentration of 10 .mu.g/ml, the percent PMN adherence declined. . . incubated with conditioned medium was 99.7%. Thus, the compounds employed in the process of this invention are particularly effective in **blocking** adherence of **leukocytes** and thereby aiding in reducing the degree of inflammation.

DETDESC:

DETD(32)

Referring to FIG. 7, lysozyme released by PMN primed with LPS-stimulated mononuclear **leukocyte** conditioned medium (containing inflammatory cytokines) and stimulated with FMLP was about 2 1 .mu.g/ml in the absence of DBOPX. When. . . .mu.g/ml. At a DBOPX concentration of 100 .mu.g/ml, the lysozyme release was only about 1.04 .mu.g/ml. The probability that DBOPX **inhibited** lysozyme release from PMN primed with conditioned medium and stimulated with FMLP was 95%.

DETDESC:

DETD(34)

In summary, the compounds of formula (I) employed in the process of this invention are capable of modulating the effects of **leukocyte** derived cytokines, such as interleukin-1 and tumor necrosis factor, on phagocytes, such as polymorphonuclear **leukocytes**. The compounds are capable of substantially aiding chemotaxis. In addition, the compounds can **block** adherence of cells. The compounds can decrease oxidative damage to host tissues by phagocytes as evidenced by modulation of respiratory burst in stimulated polymorphonuclear **leukocytes**. Finally, the compounds can modulate the effects of cytokines on degranulation in stimulated phagocytes. The demonstrated **inhibition** of IL-1, TNF, and other cytokines by these compounds is suggestive of clinical effectiveness in at least the following areas. . .

DETDESC:

DETD(35)

Because IL-1, TNF, and other **leukocyte** derived cytokines have been implicated in such a wide variety of mammalian conditions, this invention has a similarly broad scope of application. Among the conditions that can be treated or alleviated by the **inhibition** of IL-1, TNF, and other

leukocyte derived cytokines are: sepsis, septic shock, endotoxic shock, gram negative sepsis, toxic shock syndrome, adult respiratory distress, fever and myalgias. . .

DETDESC:

DETD(39)

Representative viruses are: Rhinovirus; Parainfluenza; Enterovirus; Influenza; Smallpox and vaccinia; **Herpes** simplex; Measles; Rubella; **Arbovirus** (Western, Eastern and Venezuelan equine **encephalitis**, and California **encephalitis**); Rabies; Colorado tick fever; Yellow fever; Dengue; Hepatitis Virus B (HB Ag); Hepatitis Virus A (HAV); and Human Immunodeficiency Virus. . .

DETDESC:

DETD(43)

In addition, **inhibition** of IL-1, TNF, and other **leukocyte** derived cytokines will enhance phagocyte activity in stored blood and blood products.

DETDESC:

DETD(64)

To demonstrate the effectiveness of the claimed invention, a compound of the general formula I was tested to demonstrate **inhibition** of the activity of both in vitro-generated human IL-1 and other **leukocyte** derived cytokines, and purified human IL-1. Though a variety of compounds within the general formula (I) are effective in **inhibiting** the activities of IL-1 and other **leukocyte** derived cytokines, they will be exemplified with regard to 1,3dibutyl 7-(2-oxopropyl)xanthine (DBPOX) as a particularly preferred form of the invention.

DETDESC:

DETD(75)

DBOPX increased chemotaxis **inhibited** by IL-1, TNF, or LPS stimulated mononuclear **leukocyte** conditioned medium as shown in FIGS. 1, 2 and 3.

CLAIMS:

CLMS(1)

What is claimed is:

1. A method of treating a human to **inhibit** tissue injury accompanying inflammation resulting from **leukocyte** activity induced by cytokines produced in response to an inflammatory stimulus in the human, wherein the method comprises administering to. . .
which can be substituted by a methyl group;
wherein said xanthine is administered to said human in an amount sufficient to **inhibit** activity of human interleukin-1, human tumor necrosis factor, or the activity of other human **leukocyte**-derived human cytokines on polymorphonuclear **leukocytes** or monocytes in said human to thereby **inhibit** said tissue injury.

CLAIMS:

CLMS(3)

3. A method of treating a human to **inhibit** tissue injury accompanying inflammation resulting from **leukocyte** activity induced by cytokines produced in response to an inflammatory stimulus in the human, wherein the method comprises administering to. . .
human in an amount sufficient to modulate the inflammatory effect of human interleukin-1, human tumor necrosis factor, or other human **leukocyte**-derived cytokines on polymorphonuclear **leukocytes** or monocytes by counteracting the **inhibitory** effect on cell movement in said human.

CLAIMS:

CLMS(5)

5. A method of treating a human to **inhibit** tissue injury accompanying inflammation resulting from **leukocyte** activity induced by cytokines produced in response to an inflammatory stimulus in the human, wherein the method comprises administering to. . .
which can be substituted by a methyl group;
wherein said xanthine is administered to said human in an amount sufficient to **inhibit** the stimulatory effect of human interleukin-1, human tumor necrosis factor, or other human **leukocyte**-derived cytokines or adherence of polymorphonuclear **leukocytes** or monocytes in said human to thereby **inhibit** said tissue injury.

CLAIMS:

CLMS(7)

7. A method of treating a human to **inhibit** tissue injury accompanying inflammation resulting from **leukocyte** activity induced by cytokines produced in response to an inflammatory stimulus in the human, wherein the method comprises administering to. . .
which can be substituted by a methyl group;
wherein said xanthine is administered to said human in an amount sufficient to **inhibit** stimulatory effect of human interleukin-1, human tumor necrosis factor, or other human **leukocyte**-derived human cytokines n oxidative burst of stimulated polymorphonuclear **leukocytes** in said human to thereby **inhibit** said tissue injury.

CLAIMS:

CLMS(9)

9. A method of treating a human to **inhibit** tissue injury accompanying inflammation resulting from **leukocyte** activity induced by cytokines produced in response to an inflammatory stimulus in the human, wherein the method comprises administering to. . .
which can be substituted by a methyl group;
wherein said xanthine is administered to said human in an amount sufficient to **inhibit** the activity of human interleukin-1, human tumor necrosis factor, or other human **leukocyte**-derived human cytokine on degranulation of stimulated polymorphonuclear **leukocytes** in said human to thereby **inhibit** said tissue injury.

CLAIMS:

CLMS(11)

11. A method of treating a human to **inhibit** tissue injury accompanying inflammation resulting from **leukocyte** activity induced by cytokines produced in response to an inflammatory stimulus in the human, wherein the method comprises administering to. . .
which can be substituted by a methyl group;

wherein said xanthine is administered to said human in an amount sufficient to **inhibit** the effect of human interleukin-1 or human tumor necrosis factor on oxidative burst or degranulation of stimulated neutrophils in said human to thereby **inhibit** said tissue injury.

CLAIMS:

CLMS(13)

13. . . .
which can be substituted by a methyl group;
wherein said xanthine is administered to said human in an amount sufficient to **inhibit** activity of human interleukin-1, human tumor necrosis factor, or the activity of other human **leukocyte**-derived human cytokines on polymorphonuclear **leukocytes** or monocytes in said human to thereby **inhibit** said effects.

US PAT NO: 4,215,137 [IMAGE AVAILABLE] L6: 32 of 32

DETDESC:

DETD(3)

It . . . immuno stimulants, including diseases of bacterial origin, such as leprosy caused by Mycobacterium leprae; diseases of viral origin, such as **Herpes** infections; diseases involving inflammatory conditions, such as rheumatoid arthritis, allergic **encephalitis**, lupus erythematosus, Masugi nephritis or Crohn's disease; diseases involving allergic reactions, such as allergic asthma, diseases involving protozoal infections, such. . .

DETDESC:

DETD(16)

(6) Similarly the anti-TB activities of the compounds of the invention are **blocked** by simultaneous administration of dexamethasone, an adrenocortical steroid which is known to destroy **leucocytes** [Eisen, Immunology, Harper and Row Publishers, 2nd Ed., pages 473-474 (1974)].

DETDESC:

DETD(56)

Reduction in the number of **leucocytes**, including macrophages and T-lymphocytes, in M. tuberculosis infected mice medicated with the subject compounds was also shown by studies in which subcutaneous administration of either 1 mg./kg./day or 10 mg./kg./day of dexamethasome (Dexa.) was shown to sharply **inhibit** the anti-TB activity of Compound I in comparison with either non-dexamethasone medicated controls or isoniazid-medicated animals. The data so obtained. . .

00097474

Herpes Simplex Virus in Postmortem **Multiple Sclerosis** Brain Tissue (ARTICLE)

SANDERS, VIRGINIA J.; WADDELL, AIMEE E.; FELISAN, STEPHEN L.; LI, XIMING; CONRAD, ANDREW J.; TOURTELLOTTE, WALLACE W.
Archives of Neurology 53 (2) : 125- 133 (1996)
Feb, **1996**; Original Contribution: tzn125
LINE COUNT: 00518
0003-9942

Background: Herpes simplex virus (HSV) is a common neurotropic virus that is capable of long latencies. It can cause focal demyelination in animals. Objective: To test for the presence of HSV-1 and -2 in postmortem brain samples from patients with **multiple sclerosis** (MS) and controlsusing polymerase chain reaction and Southern blot hybridization. Methods: Dissected plaque tissue classified as active or inactive and unaffected white matter (WM) and gray matter (GM) from 37 cases of MS were screened for HSV using polymerase chain reaction and Southern blot hybridization. White matter and GM from 22 cases of Alzheimer's disease, 17 cases of Parkinson's disease, and 22 cases without neurologic disease served as controls. Results: Forty-six percent (17/37) of the MS cases and 28% (17/61) of the control cases had samples that were positive for HSV (P=.11). Forty-one percent (9/22) of active plaques and 20% (6/30) of inactiveplaques were positive for HSV. Twenty-four percent (9/37) and 14% (5/37) of MS cases and 23% (14/61) and 13% (8/61) of non-MS cases hadHSV in WM and GM, respectively. No significant differences were foundamong all subgroups (P=.10). Conclusions: Herpes simplex virus was present in more MS cases thancontrol cases and in more active plaques than inactive plaques. The presence of HSV in WM and GM in cases of MS as well as in control cases makes an etiologic association to the MS disease process uncertain, but cellular localization of HSV and its relationship to oligodendrocytes and latency may reveal such an association in futurestudies. (Arch Neurol. 1996;53:125-133)

Multiple sclerosis (MS) is characterized by multifocal lesions of demyelination and inflammation./1/ Its cause remains unknown. The theory addressed in this report proposes that a virus persistent in the central nervous system (CNS) is responsible for MS; a candidate could be herpes simplex virus 1 and 2 (hereafter referred to simply as HSV).

Herpes simplex virus is a common human pathogen; 70% to 80% of the population have antibodies to HSV./2/ The hallmark characteristic of the **herpesviruses** is their capability for latency. The virus remains latent in the neurons of the trigeminal or sacral ganglia until reactivation, which results in centrifugal spread to the site of infection and possible spread into the CNS./3/ Polymerase chain reaction (PCR) detected HSV in the trigeminal ganglia in 72% of a postmortem population; all of the sampled population older than 60 years were infected./4/ The virus has also been detected in 35% of nonneurologically diseased brains./5/

Herpes simplex virus can induce multifocal demyelination in experimental animals. Inoculation with HSV-1 results in primary demyelination and inflammatory infiltrates./6,7/ Both active and inactive plaques are present in mice for prolonged periods; viral antigen and viral

DNA are not present after 21 days, although active plaques can still be seen as long as 8 weeks after inoculation./8/ Having crossed the blood-brain barrier, the virus can spread easily through the CNS./5,6,9,10/

Patients with MS have immune abnormalities suggestive of herpes infection. The elevated intrathecal IgG synthesis rate and the presence of unique CSF IgG oligoclonal bands in patients with MS are similar to those in patients who have recovered from herpes simplex encephalitis, who may also demonstrate viral antibody (both specific and nonspecific) intrathecally up to 11 years after infection./11/ A dissociation of lymphocytic response to HSV has been reported in patients with MS. Isolated MS lymphocytes were not stimulated to an activated state when challenged by HSV; whereas other viruses did induce activation of MS lymphocytes equivalent to that found in controls./12/

We propose that the demyelination seen in MS is due to different causes in different cases. A case-by-case analysis resulting in a subset of cases in which HSV is detected in active plaques would support this proposal. It is not proof of cause and effect, but rather a necessary first step. In our study, dissected MS plaques were histologically and immunocytochemically characterized for myelindebris and immunologic activity. Samples of normal-appearing white matter (WM) and gray matter (GM) from the same subjects with MS were also studied to serve as a type of control. Adjacent sections were examined by PCR and Southern blot hybridization to determine the incidence of HSV. Samples of normal-appearing WM and GM from subjectswithout MS were also studied to serve as a further control.

RESULTS

REPRODUCIBILITY AND ACCURACY CHECKS

1. The stability of viral DNA against autolytic enzymes was investigated by means of a 30-cycle PCR experiment performed on cryosections from a case of herpes simplex encephalitis stored at 4 degreesC, 25 degreesC, and 37 degreesC for 1, 2, and 7 days each. Allgroups were run in quadruplicate. Densitometric analysis of Southern-blotted amplification products showed no significant differences among the groups at different autolysis times and different temperatures, suggesting that there was no effect of autolysis time on viral DNA integrity under these conditions (Figure 4).

2. Variability of nucleic acid purification and recovery was testedby comparing the signal of three groups of samples of precisely equalstarting material. Dilutions of a herpes simplex encephalitis tissue homogenate were extracted (1:1, 1:100, and 1:10,000), and the resulting amplified product signals were compared. There were 12 tubes per group. There was no significant difference among the tubes within each group, indicating that there was no systematic variability in nucleic acid purification and recovery (Figure 5).

3. Variability of amplification efficiency within a PCR experiment and between PCR experiments was examined. Intensity of sequence-specific Southern blot bands from seven serial dilutions of HSV-1 MacIntyre strain DNA extract (one to 1000 copies per reaction) from three different PCR runs was measured. The serial dilutions wereplotted, and the equations of the resulting lines were determined. There were no differences among the determined line equations from different dilution series within a PCR experiment (Figure 6).

DETECTION OF HSV

Multiple Sclerosis

The overall incidence of cases that were positive for HSV within the entire MS group was 46% (17/37) (Table 3): 41% (9/22) of the type2 plaques, 20% (6/30) of the type 4 plaques, and 24% (9/37) and 14% (5/37) of normal-appearing WM and GM, respectively, were positive forHSV. There was no significant difference among these frequencies (P=.11).

Case-by-case analysis of the patterns of virus distribution showed that 32% (12/37) fulfilled the criteria for presence of virus in somemeaningful combination (Table 4). Three cases had virus only in type 2 plaques; three had virus in type 2 and type 4 plaques; two had virus in type 2 and type 4 plaques and in normal-appearing WM; one had virus in all sample types; one had virus in type 2 plaques and innormal-appearing WM and GM; one had virus in type 2 plaques and in normal-appearing WM; and one had

virus present in type 2 plaques and in normal-appearing GM. There were five other cases that had a variable distribution of positive signals, none of which were found in type 2 plaques.

Controls

Seventeen (28%) of 61 control cases were positive for HSV (Table 5): six (27%) of the 22 cases without neurologic disease, five (23%) of the 22 cases of Alzheimer's disease, and six (35%) of the 17 casesof Parkinson's disease. There were no significant differences among control subgroups. Among the control cases, HSV was present in 23% (14/61) of the cases in which WM was sampled and in 13% (8/61) of those in which GM was sampled. There was no significant difference between the frequency of cases with positive WM samples and cases with positive GM samples.

MS vs non-MS Controls

In the MS group, 46% of the samples were positive for HSV (Table 3); 28% of all the samples in the non-MS control group were positive for HSV (Table 5). There was no significant difference between these groups (P=.11). In the MS group, HSV was found in 24% and 14% of the WM and GM samples, respectively, and in the non-MS group, it was found in 23% and 13% of the samples. There was no significant difference between these groups either (P=.10).

Because of inherent differences in tissue type (plaque, WM, and GM)and size of sections affecting cell number per section and amount of DNA present, the association between quantity of DNA and frequency ofHSV positivity was statistically analyzed. There was no statisticallysignificant difference in the quantity of DNA and the incidence of positive signals (data not shown; P=.20). Therefore, the positive signals were not simply the result of greater DNA concentrations being used as template.

COMMENT

Our laboratory has taken precautions to avoid the inherent pitfallsassociated with the extreme sensitivity of the PCR procedure. We havedemonstrated that our detection method is reliably sensitive for detecting between one and 10 virus copies per reaction. It has beenestablished that the viral DNA does not degrade significantly andthat there is relatively little variability in nucleic acid extraction and amplification efficiency between identical specimens, suggesting that our PCR amplification is not overshadowed by random error. Hence, our methodology is sensitive, specific, reproducible, and without contamination.

MULTIPLE SCLEROSIS

We found HSV in a subset of CNS samples from both patients with MS and control patients. Seventeen (46%) of 37 cases of MS had samples that were positive for HSV. These data, analyzed on a case-by-case basis, are in keeping with our idea that there is more than one causeof MS. For a given virus to be involved in the pathogenesis of MS, itmust be present in plaque tissue. It is an expected result that individual cases may have dissimilar patterns of distribution of a candidate virus in different tissue types (Table 4). Our hypothesis predicts that HSV or other possible causative agents will be present and active in type 2 plaques, but it is also possible that latent virus will be present. In distribution patterns II, III, and IV, it is possible that some active virus will be found in type 4 plaques, but the majority will be latent. In the other distribution patterns, the virus should be in a latent phase in normal-appearing WM and GM. Future experiments will determine the latency state of the virus in each of the blocks studied.

Within the entire MS group, 41% of the active type 2 plaques were positive for HSV, whereas only 20% of the type 4 and 25% and 14% of the normal-appearing WM and GM tissue samples, respectively, were positive for HSV. Our results suggested a trend but did not show any significant differences. Perhaps the virus was not completely eradicated from the inactive lesions or that it is in a latent form in these plaques and in normal-appearing WM and GM.

Until infected cells are identified, it is not possible to determine whether the virus is a causative agent, is merely present in a latent form, or is a consequence of the immunologic activation associated with active demyelination. The higher prevalence of virus in active type 2 plaques may

be attributable to the inflammatory response occurring in the lesion site, but the 14 type 2 plaques thatwere negative for HSV (Table 3) argue against this explanation. Theseactively demyelinating plaques are without virus but contain inflammatory infiltrates similar to those in plaques with virus. Thissituation implies that the inflammation of MS per se does not bring in HSV-infected cells from the blood. These type 2 plaques without HSV could be attributable to another cause. Nevertheless, if HSV is related to the MS disease process, it is reasonable that active viruswould be found at the highest frequency in areas of immunologic activity and recent destruction of myelin.

To our knowledge, it has not been reported that HSV is found more frequently in WM than GM. In our study, the careful dissection of pure WM or GM reduced the possibility of contamination. Perhaps the sensitivity of PCR permitted the detection of low levels of HSV (either active or latent) in neurons that are located in the WM or innonneuronal cells. Astrocytes and oligodendrocytes may be infected byHSV/18-20/; other nonneuronal cells (eg, macrophages, microglia, endothelial cells, and intravascular leukocytes) may contribute to the positive signal. It is also possible that the virus is in the axon of its infected neuron located in nearby GM. On the other hand, the infected normal-appearing WM could be prelesional, where viral load is either in a latent stage or active but too low to cause distinct tissue damage.

The positive results in our cases of MS are in contrast to those ofNicoll et al,/21/ who reported that only one of the samples obtained from 23 patients with MS was positive for HSV. They used formalin-fixed, paraffin-embedded tissue and detected the amplified product with ethidium bromide, which is less sensitive than Southern blot hybridization. These differences in methodology could explain the different results.

CONTROLS

Herpes simplex virus was found in 27% of the patients without neurologic disease, in 23% of the patients with Alzheimer's disease, and in 35% of the patients with Parkinson' disease. The presence of HSV in the CNS of such a high percentage of cases is not a surprise owing to the ubiquitous and neurotropic nature of the virus. Similarly, it is not unreasonable to find HSV in tissue with no obvious disease, as is the case when the trigeminal ganglia are infected with latent virus.

Our results differ from those of other studies that have examined brain tissue for the presence of HSV using PCR. Alexander et al/22/ did not find HSV in any samples of temporal lobe tissue obtained in schizophrenic, nonschizophrenic suicide, or normal control cases. In contrast, Jamieson et al/23/ found HSV in frontal, temporal, and hippocampal tissue samples in all eight cases of AD and in six normalcontrol cases. The small size of these studies could explain the conflicting results.

Our study expands on the work by Baringer and Pisani,/5/ who reported a baseline frequency rate of HSV in 35% of nonneurologicallydiseased brains. The authors confined their search to the trigeminal ganglia, olfactory bulbs, medulla, pons, hippocampus, amygdala, gyrusrectus, calcarine cortex, and cerebellum. All the samples contained both GM and WM. Herpes simplex virus was most frequently detected in the pons, medulla, and olfactory bulbs. While an association of HSV with neurologic disease is not refuted by the authors, they caution other researchers to be conservative about interpretation of results based on frequency rates.

Our study, because of the different focus, examined cortical GM andWM primarily from the corona radiata; to our knowledge, this is the first study to discriminate between tissue types (plaque type as wellresults are in accord with those of Baringer and Pisani./5/

MS vs CONTROL CASES

Herpes simplex virus was found slightly more often in cases of MS than in control cases, although the difference was not statistically significant. It would be premature to explain this difference as proof of causation. Other explanations are compelling as well. Patients with MS are usually treated with steroids or other immunosuppressants. The immunosuppression occurring in the patients because of the medications could allow for the reactivation of the virus and travel across the blood-brain barrier. The virus may enter the brain through infected macrophages or lymphocytes that are sometimes seen in the perivascular

space of grossly normal-appearing tissue. Another possibility is that because of the different cellularmilieu, virus is technically more easily identified in type 2 plaquesand WM than in type 4 plaques and GM.

The significance of our results to MS is yet to be determined, especially in view of the high frequency of virus found in non-MS cases. However, this study is our first step in elucidating the role of HSV in the pathogenesis of MS. **Multiple sclerosis** may have many different causes, all resulting in primary demyelination. Our data support this notion, since 59% of type 2 plaques did not contain HSV,in contrast to 41% that did. A long-term goal of our laboratory is toestablish which cell or cells may be harboring a latent or active virus in the samples positive for HSV. Will oligodendrocytes in active plaques contain HSV that is expressing proteins, in contrast to inactive and normal-appearing WM and GM in which HSV is latent?

Accepted for publication October 5, 1995.

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We thank the many individuals who work in the National NeurologicalResearch Specimen Bank, especially Iris Rosario, RN, James Riehl, MT(ASCP), Peter Chun, and Randall Warwick. We also thank Diane Guntrip for administrative assistance, and Karl Syndulko, PhD, for assistance with statistical analysis.

Reprint requests to Neurology Services (127A), West Los Angeles Veterans Affairs Medical Center, 11301 Wilshire Blvd, Los Angeles, CA, 90073 (Dr Tourtellotte).

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MATERIALS AND METHODS

BRAIN SAMPLES

One hundred twenty-six postmortem brain samples from 37 patients with MS were examined. Disease duration ranged from 4 to 47 years. A total of 204 postmortem samples obtained from 22 subjects with Alzheimer's disease, 17 subjects with Parkinson's disease, and 22 subjects without neurologic disease were used as controls (Table 1 and Table 2).

TISSUE PREPARATION

All postmortem brains were received on ice and immediately cut into5-mm-thick coronal sections; a clean knife was used for each slice. Any blood remaining on the coronal section was wiped off. Sections were sealed in plastic bags and flash frozen between aluminum plates in liquid nitrogen. All specimens were stored at -70 degreesC./13/

Brain areas were dissected with separate disposable microtome blades. White matter tissue blocks did not contain any GM and vice versa. Blocks

that contained plaques did have, by necessity, some periplaque WM. Any gross-appearing GM was trimmed away. To prevent any possible contamination of blocked tissue from previously amplified PCR products and other foreign substances, approximately 100 um of each block was cryosectioned and discarded before sections were cut for PCR. A separate disposable microtome blade was used for each section. The subsequent sections were used for routine staining (hematoxylin-eosin and oil red O) and for immunocytochemical stainingfor the major histocompatibility complex class II immunologic marker HLA-DR. Each tissue sample was characterized histologically by a four-scale classification as follows/1/:

Type 1. Earliest lesion in which activated microglia are respondingto initial events of the disease process. There is no evidence of myelin breakdown. Some of these regions appear similar to microglial nodules.

Type 2. Active lesion in which microglia at the edge of the plaque are immunologically activated. Macrophages toward the center of the plaque have converted myelin debris to neutral lipid (Figure 1 and Figure 2).

Type 3. Modestly active lesion in which there is a distinct edge ofactivated microglia and macrophages. The center of the lesion is completely demyelinated.

Type 4. Least active or completely inactive lesion in which activated microglia and macrophages may be present but no neutral lipid or myelin debris remains.

In this study, we compared type 2 plaques with type4 plaques; in further studies, we will screen other plaque types. There were 22 type 2 plaques, 30 type 4 plaques, and 37 normal-appearing WM and GM samples each. Seven cases consisted of a type 2 plaque, WM, and GM; 15 cases were composed of a type 4 plaque, WM, and GM; and 15 others were made up of all tissue types. Control tissue consisted of periventricular WM and cortical GM from subjects with (1) Alzheimer'sdisease, (2) Parkinson's disease, and (3) no neurologic disease. A sample containing both GM and WM from the temporal lobe of a subject with herpes simplex encephalitis was used as a positive control.

NUCLEIC ACID EXTRACTION AND PURIFICATION

Cryosections from each block were placed in 100-uL ribonuclease-free, deoxyribonuclease-free deionized water and stored at -70 degreesC. Nucleic acids were extracted by guanidinium isothiocyanate-alkaline phenol-chloroform,/14/ followed by ethanol precipitation with glycogen as a carrier.

PRIMERS

The oligonucleotide primer sequences were 5`TTGAAGCGGTCGGCGGCGTA-3`an d 5`GCATCGTCGAGGAGGTGGA-3`(Bioserve Biotechnologies, Laurel, Md), giving a 148-base pair amplification product. This primer set is froma highly conserved region of the polymerase gene/15/ and gives a product specific for both HSV-1 and HSV-2. Primers were checked for primer-dimer formation, hairpin formation, and mispriming sites with a 4.0 primer selection software program (Oligo, National Biosciences,Plymouth, Minn). Cross-reactivity with human genomic sequences was checked by means of a BLAST (Basic Local Alignment Search Tool) search. There was no cross-reactivity of these primers with Epstein-Barr virus, cytomegalovirus, varicella-zoster virus, or humanherpesvirus 6 as determined by our using each of these viruses as template for PCR amplification and Southern blot detection and not obtaining a positive signal for any of the other viruses (data not shown).

AMPLIFICATION AND SOUTHERN BLOT DETECTION

Polymerase chain reaction amplification was carried out with the use of heat-stable Taq DNA polymerase in a total reaction volume of 100 uL containing between 0.6 and 1.0 ug of the extracted nucleic acid as a template. The optimized reaction conditions used consisted of 200-umol/L each deoxynucleotide triphosphate (2`-deoxyadenosine-

5`-triphosphate, 2`-deoxy-cytidine-5`-triphosphate, 2`-deoxy-guanosine -5`-triphosphate, and 2`-deoxy-thymidine-5`-triphosphate), 100 pmol/L of each primer, 0.01%acetylated bovine serum albumin, 1.5-mmol/L magnesium chloride, 50-mmol/L potassium chloride, 10-mmol/L TRIS (pH, 9.0), and 0.1% Triton X-100. One unit of Taq polymerase (Promega, Madison, Wis) was added in a modified `hot start' procedure using presized sterile wax beads (AmpliWax, Perkin-Elmer Corp, Norwalk, Conn). The reagents wereheated and

the Taq was added during the first thermocycling step. Thethermocycling parameters were 60 seconds at 95 degreesC, 90 seconds at 60 degreesC, and 90 seconds at 72 degreesC, and amplification was performed for 40 cycles. Thermocycling was followed by a 10-minute final extension incubation at 72 degreesC. Each specimen was run in triplicate within each thermocycling batch.

After thermocycling, 10% of each PCR-amplified product was run on a1.0% agarose gel, partially depurinated, and suction blotted onto a nylon membrane (Stratagene, La Jolla, Calif). The membranes were probed with a digoxigenin-labeled oligonucleotide fragment specific for the PCR-amplified product using the methods and reagents outlinedin the manufacturer's kit (Genius, Boehringer-Mannheim Corp, Indianapolis, Ind). After probe hybridization, the membranes were developed with alkaline phosphatase-conjugated, digoxigenin-specific antibody. Colorimetric detection was carried out with 4-nitroblue tetrazolium chloride and 5-bromo-4-chloro-indolyl-phosphate (Boehringer-Mannheim Corp). The position of probe-detected bands compared with molecular-weight markers (molecular-weight marker VI, Boehringer-Mannheim Corp) were consistent with the expected amplification product size (Figure 3).

Semiquantitation, when performed, was as follows: the membranes were digitized on a scanner (model IIc, Hewlett-Packard Co, Palo Alto, Calif) at 300 dots per inch, 256-level gray scale (eight-bit), 100% size. The image-processing software (Image 1.52, public domain software written by Wayne Rasband of the National Institutes of Health, Bethesda, Md) was used to identify and outline bands (image particles) and to quantify band area and mean band density. The product of band area and mean density gives a reliable indication of the amount of `blackness' present in a band, and was compared with a derived standard curve to give a numerical value of the copy number for each band./16/

To minimize tissue contamination, tissue preparation, nucleic acid extraction, PCR reagent preparation, and the amplification and detection procedures were performed in three separate buildings. Standard procedure dictated the use of disposable gowns and hair and shoe cov-ers for all laboratory personnel before they entered the tissue preparation laboratory. All laboratories were irradiated dailyby mercury UV lamps. Laboratory technicians were assigned to separateduties. All pipette tips, tubes, and gels used for analyzing PCR products were discarded in a waste receptacle containing a 0.1-mol/L hydrochloride solution; similarly, all nonporous surfaces within the laboratories were wiped down with diluted hydrochloride to minimize carryover into other rooms.

POSITIVE AND NEGATIVE REACTION CONTROL DESIGN

To identify and minimize the effect of false positives or false negatives, we instituted a number of quality controls on each of our experiments. To identify false-positive results (1) 25% reagent blankcontrols (double-distilled water was added instead of sample) were included in each PCR thermocycling batch; (2) 10% of all reaction tubes were true-negative controls (double-distilled water was run through the entire nucleic acid extraction procedure); (3) each specimen was run in triplicate (a specimen exhibiting only one positive was suspected of being a false positive and was rerun); and (4) 40-tube PCR batches containing 36 reagent blanks and one positivecontrol serial dilution served as a redundant check on our contamination-prevention efforts.

The following steps were taken to ensure that each PCR batch exhibited proper sensitivity:

1. A serial dilution of HSV-1 strain DNA extract of known concentration (Catalog No. 08-705-000, Advanced Biotechnologies Inc, Columbia, Md) representing one to 1000 copies per reaction was added to each PCR batch as a sensitivity control (Figure 3).

2. Nucleic acid extracted from temporal lobe tissue from a case of herpes simplex encephalitis was used as an overall positive control for each experiment.

3. Data was obtained only from (a) membranes that exhibited a PCR sensitivity of at least 10 copies per reaction, (b) all positive controls exhibiting a strong specific band, and (c) every one of the negative control and reagent blank lanes exhibiting no specific bands. All tissue specimens were coded at the time of specimen preparation and remained coded

until after all membranes in the studywere developed.

STATISTICS

The x/2/ statistic (with continuity correction as needed) was used to compare frequencies of positive signals among groups with a cutoffP value of .05./17/

Announcement

Free Patient Record Forms AvailablePatient record forms are available free of charge to Archives readers by calling or writing FORMEDIC, 12D Worlds Fair Dr, Somerset, NJ 08873-9863, telephone (908) 469-7031.

14/7/5 (Item 5 from file: 5)
DIALOG(R)File 5:BIOSIS PREVIEWS(R)

09782146 BIOSIS NO.: 199598237064
Diagnosis of **herpes** simplex **encephalitis**: Application of polymerase chain reaction to cerebrospinal fluid from brain-biopsied patients and correlation with disease.
AUTHOR: Lakeman Fred D(a); Whitley Richard J; Group The National Institute Of Allergy And Infectious Diseases Collaborative Antiviral Study
AUTHOR ADDRESS: (a)Dep. Pediatr. Microbiol. and Med., Univ. Alabama at Birmingham, 309 BBRB, 845 19th St. S. UAB St**USA
JOURNAL: Journal of Infectious Diseases 171 (4):p857-863 1995
ISSN: 0022-1899
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: Isolation of **herpes** simplex virus (**HSV**) from brain tissue after biopsy has been considered the reference standard for the diagnosis of **herpes** simplex **encephalitis** (**HSE**). During the evaluation of antiviral treatment of **HSE**, cerebrospinal fluid (CSF) was obtained from patients with clinical disease indicative of **HSE** who underwent diagnostic brain biopsy. **HSV** DNA was detected by polymerase chain reaction (PCR) in CSF of 53 (98%) of 54 patients with biopsy-proven **HSE** and was detected in all 18 CSF specimens obtained before brain biopsy from patients with proven **HSE**. Four of 19 CSF specimens were positive after 2 weeks of antiviral therapy. Positive results were found in 3 (6%) of 47 patients whose brain tissue was culture-negative. Detection of **HSV** DNA in the CSF correlated significantly with age and focal radiographic findings. Thus, PCR detection of **HSV** DNA should be the standard for

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? s vla(w)4 and arbovirus

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          3338  VLA(W)4
         19446  ARBOVIRUS
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...completed examining records
     S6      2  RD S5 (unique items)
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 6/7/1     (Item 1 from file: 5)
DIALOG(R)File   5:Biosis Previews(R)
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10758578   BIOSIS NO.: 199799379723
Therapy with antibody against leukocyte integrin VLA-4 (CD49d)
  is effective and safe in virus-facilitated experimental allergic
  encephalomyelitis.
AUTHOR: Soilu-Hanninen M(a); Roytta M; Salmi A; Salonen R
AUTHOR ADDRESS: (a)Dep. Virology, Univ. Turku, Kiinamyllynkatu 13,
  FIN-20520 Turku**Finland
JOURNAL: Journal of Neuroimmunology  72 (1):p95-105 1997
ISSN: 0165-5728
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: Experimental allergic encephalomyelitis (EAE) is facilitated in
  resistant BALB/c mice by intraperitoneal infection with an avirulent
  Semliki Forest virus (SFV-A7). Viral infection increases the incidence of
  EAE from 15-30% to 60-90% and speeds up appearance of paralysis from 24
  to 14 days. In this paper, we describe treatment of virus-facilitated EAE
  with monoclonal antibodies (mAbs) against leukocyte and/or endothelial
  cell adhesion molecules. Therapy with mAb against ICAM-1 (intercellular
  adhesion molecule-1) had a modest effect, but caused hemorrhagic brain
  and spinal cord lesions. Therapy with mAb against Mac-1 (alpha-M
  beta-2-integrin) was well tolerated but had no effect. Therapy with mAb
  against VLA-4 (alpha-4-beta-1-integrin) was safe, diminished
  both clinical and histopathological signs of EAE, decreased induction of
  VCAM-1 (vascular cell adhesion molecule-1) on brain vessels and
  diminished infiltration of VLA-4+ cells into the brain. The
  amount of viral antigen in the brain was riot altered. We conclude that
  facilitation of leukocyte entry into the brain is a major mechanism for
  viral facilitation of EAE in the BALB/c mouse, and that facilitation can
  be inhibited by anti-adhesion therapy. This may have implications for
  treatment of relapses triggered by viral infections in multiple
  sclerosis.


 6/7/2     (Item 2 from file: 5)
DIALOG(R)File   5:Biosis Previews(R)
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10451484   BIOSIS NO.: 199699072629
Therapy with antibody against leukocyte integrin VLA-4 is
  effective and safe in virus facilitated EAE.
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AUTHOR: Soilu-Hanninen Merja; Roytta Matias; Salmi Aimo; Salonen Reijo
AUTHOR ADDRESS: Dep. Virol., Univ. Turku, Kiinamyllynkatu 13, 20520 Turku **Finland
JOURNAL: Scandinavian Journal of Immunology 43 (6):p727 1996
CONFERENCE/MEETING: XXVIIth Meeting of the Scandinavian Society for Immunology Turku, Finland May 24-27, 1996
ISSN: 0300-9475
RECORD TYPE: Citation
LANGUAGE: English

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? s (herpes or hsv?) and encephalitis

          115780  HERPES
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           48289  ENCEPHALITIS
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            6758  S1
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          130341  SCLEROSIS
           58051  MULTIPLE(W)SCLEROSIS
      S2     170  S1 AND (MULTIPLE(W)SCLEROSIS)
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             170  S2
         2655524  REVIEW?
      S3      13  S2 AND REVIEW?
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      S4      12  RD S3 (unique items)
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 4/7/1     (Item 1 from file: 5)
DIALOG(R)File   5:BIOSIS PREVIEWS(R)
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07599107   BIOSIS NO.: 000040110601
IMAGING OF THE CENTRAL NERVOUS SYSTEM IN INFANTS AND CHILDREN
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AUTHOR: FAERBER E N
AUTHOR ADDRESS: ST. CHRISTOPHER'S HOSP. CHILDREN, ERIE AVE. AT FRONT ST., PHILADELPHIA, PA. 19134-1095.
JOURNAL: CURR OPIN PEDIATR 3 (1). 1991. 4-11.
CODEN: COPEE
DOCUMENT TYPE: Review
RECORD TYPE: Citation
LANGUAGE: ENGLISH

4/7/2 (Item 2 from file: 5)
DIALOG(R)File 5:BIOSIS PREVIEWS(R)

02950596 BIOSIS NO.: 000069058714
HERPES SIMPLEX VIRUS AND RECURRENT LARYNGEAL NERVE PARALYSIS A CASE AND **REVIEW** OF THE LITERATURE
AUTHOR: MAGNUSSEN C R; PATANELLA H P
AUTHOR ADDRESS: ST. MARY'S HOSP., 89 GENESEE ST., ROCHESTER, N.Y. 14611, USA.
JOURNAL: ARCH INTERN MED 139 (12). 1979. 1423-1424.
FULL JOURNAL NAME: Archives of Internal Medicine
CODEN: AIMDA
RECORD TYPE: Abstract
LANGUAGE: ENGLISH

ABSTRACT: A 61 yr old man experienced abrupt onset of a non-specific febrile illness followed by the acute development of bilateral vocal cord paralysis. There was no evidence for Guillain-Barre syndrome, **multiple sclerosis**, brainstem **encephalitis**, myasthenia gravis, metabolic encephalopathy, poliomyelitis, diphtheria, botulism, tumor, vasculitis or extrinsic nerve compression. No cause for the fever was ascertained and the vocal cord paralysis improved spontaneously. Acute and convalescent viral serological studies demonstrated a diagnostic complement-fixation antibody titer rise to **herpes** simplex virus (**HSV**) and no rise in titer to influenza A and B, cytomegalovirus, poliomyelitis or Mycoplasma. This case is similar to several others that suggest viral neuritis may be involved in 10th nerve paralyses in children. Difficulties involved in diagnosing **HSV** CNS disease before death are discussed. **HSV** may be the etiological agent in selected cranial neuropathies.

4/7/3 (Item 1 from file: 73)
DIALOG(R)File 73:EMBASE

07645071 EMBASE No: 1999135220
The clinical implications of human herpesvirus 6 infection
Bremner J.A.G.; Clark D.A.
J.A.G. Bremner, Sheffield Virology Services, Department of Microbiology, Royal Hallamshire Hospital, Sheffield S10 2JF United Kingdom
Reviews in Medical Microbiology (REV. MED. MICROBIOL.) (United Kingdom) 1999, 10/1 (11-18)
CODEN: RMEME ISSN: 0954-139X
DOCUMENT TYPE: Journal; Review
LANGUAGE: ENGLISH SUMMARY LANGUAGE: ENGLISH
NUMBER OF REFERENCES: 55

Since human herpesvirus (HHV) type 6 was first discovered 12 years ago, molecular diagnostic techniques have extended our knowledge and raised new questions about the clinical implications of infection with this virus. Two subgroups of the virus exist, variant A and variant B, the latter being the predominant type detected in the US, Europe and Japan. HHV-6 infection occurs early in life, usually within the first 2 years. Within this age group, HHV-6B has been shown to cause febrile illness, including exanthem

subitum (ES), with convulsions a common complication. Evidence that HHV-6A causes ES is limited to case reports. Reactivation of HHV-6 is frequent in transplant recipients in whom there is increasing evidence that the virus is pathogenic. In bone marrow transplant recipients HHV-6 has been associated with a range of clinical syndromes including marrow suppression, pneumonitis, graft versus host disease and **encephalitis**. The role of HHV-6 in HIV disease is unclear although a number of mechanisms by which HHV-6 upregulates HIV have been described in vitro. There is growing interest in the neurological sequelae of HHV-6 infection and the central nervous system is one site of persistence. In particular, HHV-6 proteins have been detected in oligodendrocytes in plaque regions of **multiple sclerosis** (MS) brain tissue and viral DNA has been detected in sera of patients with the relapsing-remitting course of disease. However, any role that HHV-6 may play in MS pathogenesis remains to be defined. A fuller understanding of the clinical relevance of HHV-6 would facilitate the design of antiviral therapies to prevent or treat disease.

4/7/4 (Item 2 from file: 73)
DIALOG(R)File 73:EMBASE

07451088 EMBASE No: 1998369471
Human herpesvirus-6: Neurologic implications of a newly-described viral pathogen
Kimberlin D.W.; Whitley R.J.
D.W. Kimberlin, 1600 Seventh Avenue South, Birmingham, AL 35233 United States
Journal of NeuroVirology (J. NEUROVIROL.) (United Kingdom) 1998, 4/5 (474-485)
CODEN: JNVIF ISSN: 1355-0284
DOCUMENT TYPE: Journal; Review
LANGUAGE: ENGLISH SUMMARY LANGUAGE: ENGLISH
NUMBER OF REFERENCES: 130

Discovered only 12 years ago, human herpesvirus-6 (HHV-6) has been associated with central nervous system (CNS) findings such as febrile seizures, **encephalitis**, meningitis, and possibly **multiple sclerosis**. These manifestations have been reported in both immunocompetent and immunocompromised individuals. The applications of such sophisticated laboratory tools as polymerase chain reaction, in situ hybridization, immunohistochemical staining, and representational difference analysis have expanded knowledge of the spectrum of CNS disease attributable to HHV-6 while delineating pathogenic mechanisms of both primary HHV-6 infection and reactivation from latency. This article **reviews** existing knowledge of the CNS manifestations of HHV-6, focusing on both clinical aspects of HHV-6 infection and its pathogenesis on neurologic diseases.

4/7/5 (Item 3 from file: 73)
DIALOG(R)File 73:EMBASE

04726245 EMBASE No: 1991219599
Neurology
Gale A.N.; Gibbs J.M.; Schapira A.H.V.; Thomas P.K.
Dept. of Neurological Science, R/Free Hospital Sch. of Medic., Rowland Hill Street,London NW3 2PF United Kingdom
Postgraduate Medical Journal (POSTGRAD. MED. J.) (United Kingdom) 1991, 67/788 (509-531)
CODEN: PGMJA ISSN: 0032-5473
DOCUMENT TYPE: Journal; Review
LANGUAGE: ENGLISH

4/7/6 (Item 4 from file: 73)
DIALOG(R)File 73:EMBASE

04217820 EMBASE No: 1990100362
Demyelinating, inflammatory and degenerative diseases of the brain
Hourihan M.D.
Department of Radiology, University Hospital of Wales, Cardiff United Kingdom
Current Opinion in Neurology and Neurosurgery (CURR. OPIN. NEUROL. NEUROSURG.) (United Kingdom) 1989, 2/6 (870-877)
CODEN: CNENE ISSN: 0951-7383
DOCUMENT TYPE: Journal; Review
LANGUAGE: ENGLISH

4/7/7 (Item 5 from file: 73)
DIALOG(R)File 73:EMBASE

01706462 EMBASE No: 1980074736
Herpes simplex virus and recurrent laryngeal nerve paralysis. Report of a case and **review** of the literature
Magnussen C.R.; Patanella H.P.
Infect. Dis. Unit, St Mary's Hosp., Rochester, N.Y. 14611 United States
Archives of Internal Medicine (ARCH. INTERN. MED.) (United States) 1979, 139/12 (1423-1424)
CODEN: AIMDA
DOCUMENT TYPE: Journal
LANGUAGE: ENGLISH

A 61-year-old man experienced the abrupt onset of a nonspecific febrile illness followed by the acute development of bilateral vocal cord paralysis. There was no evidence for Guillain-Barre syndrome, **multiple sclerosis**, brainstem **encephalitis**, myasthenia gravis, metabolic encephalopathy, poliomyelitis, diphtheria, botulism, tumor, vasculitis, or extrinsic nerve compression. No cause for the fever was ascertained, and the vocal cord paralysis improved spontaneously. Acute and convalescent viral serological studies demonstrated a diagnostic complement-fixation antibody titer rise to **herpes** simplex virus (**HSV**) and no rise in titer to influenza A and B, cytomegalovirus, poliomyelitis, or Mycoplasma. This case is similar to several others reported in the literature that suggest a viral neuritis in tenth nerve paralyses in children. The difficulties involved in diagnosing **HSV** CNS disease before death are discussed, and the medical literature is reveiwed for evidence that **HSV** is the etiological agent in selected cranial neuropathies.

4/7/8 (Item 6 from file: 73)
DIALOG(R)File 73:EMBASE

00677233 EMBASE No: 1977022568
Slow viral encephalitides and encephalopathies (Rumanian)
Draganescu N.; Cajal N.
Str. Gutenberg Nr 3 Bis, Sectorul 6, Bucuresti Romania
1974, (235 p.)
CODEN: BOOKA
DOCUMENT TYPE: Book
LANGUAGE: ROMANIAN

The work on 'Slow viral encephalitides and encephalopathies' includes in its pages the discoveries made in this field during the last 10 years. This group of diseases has drawn the attention of research workers since the discovery of Kuru, a chronic, apparently heredo familial disorder,

occurring in the Fore people of New Guinea. The studies undertaken by Gajdusek and Gibbs on several subacute and chronic diseases supplied sensational data demonstrating the possibility that viruses 'masked or hidden for years, even decades, may be reactivated to cause chronic progressive disease, and that strange new viruses, apparently unrelated to previously known viruses, may remain inapparent in man for enormously long incubation periods, yet finally produce subacute fatal disease'. On the ground of the experimental results obtained mainly by Gajdusek and Gibbs it was concluded that other human or animal diseases, besides Kuru, might also be classified in the group of slow viral infections. Among these diseases with subacute and chronic evolution, we mention; in men, Creutzfeldt Jakob's disease, subacute sclerosing panencephalitis (SSPE), multifocal progressive leukoencephalopathy, chronic viral **encephalitis** with focal epilepsy or continuous partial epileptic syndrome, neonatal or intrauterine infection with rubella and cytomegalic viruses, subacute herpetic **encephalitis** and **herpes** zoster, and in animals, scrapie, vison encephalopathy, Visna disease, equine encephalomyelitis, hardpad of dogs and other chronic forms of distemper, and encephalomyelitis (Russian spring summer **encephalitis** in the monkey, Kyasanur forest disease in the mouse). The similarities between Kuru, Creutzfeldt Jakob's disease, scrapie and vison encephalopathy made Gajdusek and Gibbs include these diseases in the group of 'subacute spongiform viral encephalopathies'. The present work **reviews** the data available up to now on human degenerative diseases of the central nervous system, with a subacute or chronic evolution and an established viral etiology (Kuru, Creutzfeldt Jakob's disease, SSPE, multifocal progressive leukoencephalopathy, viral chronic **encephalitis** with focal epilepsy or the partial continuous epilepsy syndrome), as well as on the group of neurological diseases whose viral etiology is still questionable (Vilyuinsk **encephalitis**, amyotrophic lateral sclerosis and **multiple sclerosis**). On the other hand, data concerning the group of animal degenerative chronic nervous system diseases with an established viral etiology (scrapie, vison encephalopathy and Visna) are presented. All the above mentioned diseases are analysed from the clinical and morphopathological viewpoint and as regards their natural transmission, experimental infection, etc., emphasizing the characteristics of the viruses isolated. The material represents a synthesis of both the works published by the inexhaustible Dr. Gajdusek as well as by Drs. Gibbs, Klazo, Beck, Alpers Lampert, Bouteille, Baublis, Oyanagi, Adels, Legg, Brown, Hirano, Hadlow, Haig, Hunter, Pattison, Zlotnik, Burger, Dayan, Thormar, Leader, Helmboldt, Zilber, etc. and of some papers of ours, to which have also contributed Drs. Maria Cepleanu, C. Cernescu, St. M. Dumitrescu, Fl. Nereantiu, Elena Girjabu and Yolanda Sorodoc.

4/7/9 (Item 7 from file: 73)
DIALOG(R)File 73:EMBASE

00509701 EMBASE No: 1976065248
Slow virus infections of the nervous system in humans mainly from the neuropathological viewpoint. With special reference to comparison of so called slow transmissible disease group to encephalomyelitides with conventional virus infections (Japanese)
Shiraki H.
Dept. Neuropathol., Inst. Brain Res., Univ. Tokyo Sch. Med., Tokyo Japan
Advances in Neurological Sciences (ADV. NEUROL. SCI.) 1975, 19/1 (109-147)
CODEN: SKNSA
DOCUMENT TYPE: Journal
LANGUAGE: JAPANESE

4/7/10 (Item 8 from file: 73)
DIALOG(R)File 73:EMBASE

00191824 EMBASE No: 1974181961
Multiple Sclerosis; Immunology, Virology, and Ultrastructure; Proceedings of a Symposium at Santa Barbara, February 1972
UCLA FORUM IN MEDICAL SCIENCES; NO. 16
Wolfgram F.; Ellison G.W.; Stevens J.G.; Andrews J.M.
United States
1972, (607 p.) *pD 19.50/-
CODEN: BOOKA
DOCUMENT TYPE: Book
LANGUAGE: ENGLISH

This book includes the proceedings and discussion of a symposium. The chapters contain a **review** of up to date knowledge in the field: clinical, ultrastructural, neuropathologic, virologic, epidemiologic, serologic, pathophysiologic and chemical. The role of virus infections (**herpes** simplex, parainfluenza, and progressive pneumonia) is analysed in so far as these infections are pertinent to the pathogenesis of **multiple sclerosis** and quite a few chapters are devoted to the immunological facets of the problem.

4/7/11 (Item 1 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

09067662 97257355
[Progress of the therapy for virus related neurological disorders]
Harukawa H; Yuasa T
Department of neurology, National center of Neurology and Psychiatry, Kohnodai Hospital.
Nippon Rinsho (JAPAN) Apr 1997, 55 (4) p959-66, ISSN 0047-1852 Journal Code: KIM
Languages: JAPANESE Summary Languages: ENGLISH
Document type: JOURNAL ARTICLE; REVIEW; REVIEW LITERATURE English Abstract
In this **review** of the therapy of infectious diseases and immune mediated nervous system diseases, we summarized the latest reports of antiviral drugs, immunosuppressants, immuno-modulatory and anti-inflammatory agents. Those include, acyclovir, vidarabine for **herpes** simplex **encephalitis**, ganciclovir for cytomegaro virus infection, inosine pranobex for SSPE, steroid therapy, interferon, plasma exchange and high-dose intravenous gamma globulin therapy for HTLV-I associated myelopathy, and **multiple sclerosis** . Diagnostic application of the PCR and the newly developed neuroimaging techniques, like diffusion weighted MRI, high speed MRI, and SPECT, we now being introduced to enable early recognition of viral infection of the CNS. And since speed of spread of HIV infection through the world, we are needed specific treatment for HIV infection, and various studies including genetic therapy is going on today. (26 Refs.)

4/7/12 (Item 2 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

04374543 82180965
Experimental models of virus-induced demyelination of the central nervous system.
Dal Canto MC; Rabinowitz SG
Ann Neurol (UNITED STATES) Feb 1982, 11 (2) p109-27, Journal Code: 6AE
Contract/Grant No.: NS-13011, NS, NINDS; NS-13045, NS, NINDS
Languages: ENGLISH
Document type: JOURNAL ARTICLE; REVIEW
One of the arguments in favor of a viral pathogenesis for **multiple**

sclerosis is the existence of several experimental and natural animal models of virus-induced primary demyelination. This **review** deals comprehensively with such models. Well-known examples of demyelinating viral infections in their natural host are JHM, Theiler, visna, and canine distemper encephalomyelitides. Recent reports of experimental murine infections with pathogens such as vesicular stomatitis, Chandipura, **herpes** simplex, Venezuelan equine encephalomyelitis, and Semliki Forest viruses are also discussed. The thrust of the **review** is to include viral models suspected of producing primary demyelination on an immunopathological basis. (100 Refs.)

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 s (herpes) and (encephalitis)

          115721  HERPES
           48261  ENCEPHALITIS
      S5    6717  (HERPES) AND (ENCEPHALITIS)
? s (herpes) and (encephalitis) and (leukocyt? or leucocyt? or lymphocyt?)

          115721  HERPES
           48261  ENCEPHALITIS
          340880  LEUKOCYT?
           42278  LEUCOCYT?
          928666  LYMPHOCYT?
      S6     422  (HERPES) AND (ENCEPHALITIS) AND (LEUKOCYT? OR LEUCOCYT?
                  OR LYMPHOCYT?)
? s (herpes) and (encephalitis) and (leukocyt? or leucocyt? or
lymphocyt?)(30n)(inhibit? or suppress? or antagoni?)

Processing
          115721  HERPES
           48261  ENCEPHALITIS
          340880  LEUKOCYT?
           42278  LEUCOCYT?
          928666  LYMPHOCYT?
         3007272  INHIBIT?
          588141  SUPPRESS?
          795875  ANTAGONI?
          152797  ((LEUKOCYT? OR LEUCOCYT?) OR LYMPHOCYT?)(30N)((INHIBIT?
                  OR SUPPRESS?) OR ANTAGONI?)
      S7      19  (HERPES) AND (ENCEPHALITIS) AND (LEUKOCYT? OR LEUCOCYT?
                  OR LYMPHOCYT?)(30N)(INHIBIT? OR SUPPRESS? OR ANTAGONI?)
? rd s7

...completed examining records
      S8      14  RD S7 (unique items)
? t s8/7/all


 8/7/1     (Item 1 from file: 5)
DIALOG(R)File   5:Biosis Previews(R)
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07999808   BIOSIS NO.: 000093055481
SIGNIFICANCE OF APOLIPOPROTEIN E DETERMINATION IN PLASMA AND CEREBROSPINAL
  FLUID IN VARIOUS NEUROLOGICAL DISORDERS
AUTHOR: FURIYA Y
AUTHOR ADDRESS: DEP. NEUROL., TOKYO WOMEN'S MED. COLL.
JOURNAL: J TOKYO WOMEN'S MED COLL 61 (10-11). 1991. 977-987.
FULL JOURNAL NAME: Journal of Tokyo Women'S Medical College
CODEN: TJIZA
RECORD TYPE: Abstract
LANGUAGE: JAPANESE

ABSTRACT: It is well known that apolipoprotein E (Apo E), an important
  mediator of liquid transport and metabolism, is secreted by non-neural
  cells, such as astrocyte in the central nervous systems and macrophages
  in the peripheral nervous systems, in response to nerve injuries. Plasma
  Apo E play a role in the transport of myelin lipids in preparation for
  remyelination. For this study, Apo E and albumin concentrations in serum
  and cerebrospinal fluid (CSF) were determined and the CSF Apo E index was
  calculated in 65 patients with neurological disorders. The diagnosis
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included demyelinating diseases such as multiple sclerosis (MS), acute disseminated encephalomyelitis (ADEM), Guillain-Barre syndrome (GBS). Fisher syndromes and chronic inflammatory demyelinating polyneuritis (CIDP) as well as a variety of other neurological diseases such as cerebrovascular disorders (CVD), **herpes** simplex **encephalitis** (HSVE), aseptic meningitis, tuberculous meningitis and mycotic meningitis. Seventeen normal controls were also studied. CSF Apo E was increased in patients with MS, ADEM, GBS, CIDP, Fisher syndrome and CVD indicating either primary or secondary demyelination. Serum Apo E was decreased in all of the forementioned demyelinating diseases. The low levels of Apo E were presumed to reflect some degree of immunosuppression as Apo E concentration below 20 mg/l have been demonstrated to **suppress lymphocyte**-mediated immunofunction. The decreased serum Apo E and increased CSF Apo E seen in the demyelinating diseases produced an elevation in the Apo E index. In following the clinical course of a patient with MS, we found that serum Apo E decreased and CSF Apo E increased during exacerbations, while the converse, a decrease in CSF Apo E and an increase in serum Apo E, occurred during remissions. Similar changes were seen in a patient with GBS. A patient with mycotic meningitis initially had a slightly depressed serum Apo E level which rose remarkably during remission and had returned to normal by the time the patient was fully recovered. To elevated serum Apo E concentration seemed to be related to changes in lymphocyte-mediated immunofunction.

8/7/2 (Item 2 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

06764568 BIOSIS NO.: 000088074001
EFFECTS OF SELECTIVE DEPLETION OF L3T4-POSITIVE T-LYMPHOCYTES ON **HERPES** SIMPLEX VIRUS **ENCEPHALITIS**
AUTHOR: ERLICH K S; WOFSY D; DIX R D; MILLS J
AUTHOR ADDRESS: DIV. INFECTIOUS DIS., SAN FRANCISCO GEN. HOSP., BUILD. 80, WARD 84, 995 POTRERO AVE., SAN FRANCISCO, CALIF. 94110.
JOURNAL: CLIN IMMUNOL IMMUNOPATHOL 52 (2). 1989. 190-201.
FULL JOURNAL NAME: Clinical Immunology and Immunopathology
CODEN: CLIIA
RECORD TYPE: Abstract
LANGUAGE: ENGLISH

ABSTRACT: The L3T4 surface molecule defines a subset of murine lymphocytes which are homologous to CD4+ lymphocytes in humans, and are functionally characterized as "helper/inducer" cells. To determine the role of helper/inducer lymphocytes in the host defense against **herpes** simplex virus type 1 (HSV-1) **encephalitis**, we utilized a monoclonal antibody to selectively deplete L3T4+ **lymphocytes** from BALB/c mice prior to experimental HSV infection. Susceptibility to HSV wa only minimally increased by the depletion of L3T4 cells, although mice receiving anti-L3T4 were profoundly immuno-**suppressed**; splenic **lymphocytes** did not respond to stimulation by virus antigen in vitro, and L3T4+ **lymphocyte**-depleted mice failed to produce antibodies to HSV-1. However, mice receiving anti-L3T4 had a prolonged increase in natural killer cell activity following HSV infection as compared to controls. These data demonstrate that L3T4+ **lymphocytes** contribute minimally to host resistance to acute neural HSV infection, even though elimination of these **lymphocytes** markedly **inhibits** the genesis of immune responses.

8/7/3 (Item 3 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

06670657 BIOSIS NO.: 000087112834
ANTIHERPES ACTIVITY OF THE IMMUNOMODULATOR OK-432 A STREPTOCOCCAL

PREPARATION IN IMMUNOSUPPRESSED MICE
AUTHOR: IKEDA S; SAI K; NISHIMURA C; YAMAMOTO A
AUTHOR ADDRESS: DEP. VIROL. IMMUNOL., SCH. PHARM. SCH., KITASATO UNIV., 5-9-1, SHIROKANE, MINATO-KU, TOKYO 108, JPN.
JOURNAL: ANTIVIRAL RES 10 (6). 1988. 299-304.
FULL JOURNAL NAME: Antiviral Research
CODEN: ARSRD
RECORD TYPE: Abstract
LANGUAGE: ENGLISH

ABSTRACT: The antiviral activity of OK-432, an antitumor agent originating from Streptococcal preparations, against **herpes** simplex virus type 2 (HSV-2) was investigated in mice immunosuppressed by cylophosphamide (CY). Intraperitoneal administration of OK-432 to mice 1 day after treatment with 200 mg CY/kg prevented death due to HSV-2 **encephalitis** in a dose-dependent manner. When the immunosuppressed mice were given OK-432 prior to HSV-2 infection, both by the intraperitoneal route, virus growth in the peritoneal cavity was significantly **suppressed**. Following with OK-432, the number of macrophages in immunosuppressed mice was increased to a significantly greater extent than the number of **lymphocytes** and polymorphonuclear **leukocytes**. The intrinsic antiviral activity of macrophages against HSV-2 as well as the natural killer (NK) activity against YAC-1 target cells was significantly enhanced by OK-432 in immunosuppressed mice.

8/7/4 (Item 1 from file: 73)
DIALOG(R)File 73:EMBASE

07924572 EMBASE No: 1999397923
Chronic brain inflammation and persistent **herpes** simplex virus 1 thymidine kinase expression in survivors of syngeneic glioma treated by adenovirus-mediated gene therapy: Implications for clinical trials
Dewey R.A.; Morrissey G.; Cowsill C.M.; Stone D.; Bolognani F.; Dodd N.J.F.; Southgate T.D.; Klatzmann D.; Lassmann H.; Castro M.G.; Lowenstein P.R.
P.R. Lowenstein, Molec. Med. and Gene Therapy Unit, Stopford Building, School of Medicine, Manchester M13 9PT United Kingdom
AUTHOR EMAIL: lowenstein@man.ac.uk
Nature Medicine (NAT. MED.) (United States) 1999, 5/11 (1256-1263)
CODEN: NAMEF ISSN: 1078-8956
DOCUMENT TYPE: Journal; Article
LANGUAGE: ENGLISH SUMMARY LANGUAGE: ENGLISH
NUMBER OF REFERENCES: 45

The long-term consequences of adenovirus-mediated conditional cytotoxic gene therapy for gliomas remain uncharacterized. We report here detection of active brain inflammation 3 months after successful **inhibition** of syngeneic glioma growth. The inflammatory infiltrate consisted of activated macrophages/microglia and astrocytes, and T **lymphocytes** positive for leucosyalin, CD3 and CD8, and included secondary demyelination. We detected strong widespread **herpes** simplex virus 1 thymidine kinase immunoreactivity and vector genomes throughout large areas of the brain. Thus, patient evaluation and the design of clinical trials in ongoing and future gene therapy for brain glioblastoma must address not only tumor-killing efficiency, but also long-term active brain inflammation, loss of myelin fibers and persistent transgene expression.

8/7/5 (Item 2 from file: 73)
DIALOG(R)File 73:EMBASE

06025980 EMBASE No: 1995056148
Progressive immunodeficiency and fatal pneumonitis associated with human

herpesvirus 6 infection in an infant
Knox K.K.; Pietryga D.; Harrington D.J.; Franciosi R.; Carrigan D.R.
Department of Pathology, Medical College of Wisconsin, 8700 West Wisconsin Avenue,Milwaukee, WI 53226 United States
Clinical Infectious Diseases (CLIN. INFECT. DIS.) (United States) 1995, 20/2 (406-413)
CODEN: CIDIE ISSN: 1058-4838
DOCUMENT TYPE: Journal; Article
LANGUAGE: ENGLISH SUMMARY LANGUAGE: ENGLISH

Human herpesvirus 6 (HHV-6), an important opportunistic pathogen in immunocompromised patients, causes fatal pneumonitis, **encephalitis**, and bone marrow **suppression**. Its ability to infect and destroy T **lymphocytes** may allow it to synergize with the human immunodeficiency virus in the destruction of lymphoid tissues in patients with AIDS. We describe herein an infant who had an immunodeficiency associated with thymic atrophy and severe T lymphocytopenia who developed fatal pneumonitis due to HHV-6. Dense and disseminated infection oft lymphocytes with HHV-6 was also documented. In the absence of any other documented cause of immunodeficiency, we hypothesize that congenital infection of this infant with HHV-6 may have caused progressive destruction of her cellular immune system. leading to the fatal pneumonitis. Thus, HHV-6 infection may have been the cause of both her immunodeficiency and her fatal opportunistic infection.

8/7/6 (Item 3 from file: 73)
DIALOG(R)File 73:EMBASE

04008789 EMBASE No: 1989177785
Effects of selective depletion of L3T4sup + T-lymphocytes on **herpes** simplex virus **encephalitis**
Erlich K.S.; Wofsy D.; Dix R.D.; Mills J.
Department of Medicine, University of California, San Francisco, CA 94143 United States
Clinical Immunology and Immunopathology (CLIN. IMMUNOL. IMMUNOPATHOL.) (United States) 1989, 52/2 (190-201)
CODEN: CLIIA ISSN: 0090-1229
DOCUMENT TYPE: Journal
LANGUAGE: ENGLISH SUMMARY LANGUAGE: ENGLISH

The L3T4 surface molecule defines a subset of murine lymphocytes which are homologous to CD4sup + lymphocytes in humans, and are functionally characterized as 'helper/inducer' cells. To determine the role of helper/inducer lymphocytes in the host defense against **herpes** simplex virus type 1 (HSV-1) **encephalitis**, we utilized a monoclonal antibody to selectively deplete L3T4sup + lymphocytes from BALB/c mice prior to experimental HSV infection. Susceptibility to HSV was only minimally increased by the depletion of L3T4sup + cells, although mice receiving anti-L3T4 were profoundly immunosuppressed; splenic lymphocytes did not respond to stimulation by virus antigen in vitro, and L3T4sup + lymphocyte-depleted mice failed to produce antibodies to HSV-1. However, mice receiving anti-L3T4 had a prolonged increase in natural killer cell activity following HSV infection as compared to controls. These data demonstrate that L3T4sup + **lymphocytes** contribute minimally to host resistance to acute neural HSV infection, even though elimination of these **lymphocytes** markedly **inhibits** the genesis of immune responses.

8/7/7 (Item 4 from file: 73)
DIALOG(R)File 73:EMBASE

01682338 EMBASE No: 1980113692
Assay of interferon and viral antibodies in the cerebrospinal fluid in

clinical neurology and psychiatry
Libikova H.; Breier S.; Kocisova M.; et al.
Inst. Virol., Slovak Acad. Sci., Bratislava Czechoslovakia
Acta Biologica et Medica Germanica (ACTA BIOL. MED. GER.) (Germany)
1979, 38/5-6 (879-893)
CODEN: ABMGA
DOCUMENT TYPE: Journal
LANGUAGE: ENGLISH

Cerebrospinal fluid (CSF) of 245 neurological and 194 psychiatric patients were tested for viral antibodies and interferon. Complement dependent neutralizing antibodies to **Herpes** virus hominis 1 were found in the CSF of patients with **encephalitis** (50.6%), meningitis (35.4%), lesions of peripheral nerves (36.9%), sclerosis multiplex (41.2%), schizophrenia (31.9%), senile dementia (51.4%), mental retardation (11.1%), ethylism (43.5%). Neutralizing antibodies to tick-borne **encephalitis** virus were found in the CSF of 38% patients with **encephalitis**, in 14% meningitis, 11% lesions of peripheral nerves and also in 5.6-11.8% of psychiatric patients. In **encephalitis**, meningitis and in lesions of peripheral nerves, plaque neutralizing antibodies to the tick-borne orbivirus Lipovnik, complement-fixing antibodies to **lymphocytic** choriomeningitis virus and hemagglutination **inhibiting** antibodies to measles virus were frequently found in the CSF. In multiple sclerosis CSF antibodies to measles virus (44%) were detected, **Herpes** virus hominis 1 (41.2%) and Lipovnik virus (52.6%). In neurological patients CSF antibodies were observed simultaneously to two or three viruses in 16.7 to 40.6%, while in psychiatric patients in zero to 4.6%. CSF interferon was found in psychiatric patients with an equal or even higher incidence (33.7 to 57.1%) than in the neurological patients (29.6-38.6%, in multiple sclerosis only 16.7%). Non-interferon virus inhibitors were excluded. The evaluation of the ratio of serum and CSF titers of viral antibodies and of interferon indicated local synthesis of both in the central nervous system - with the exception of antibodies to **Herpes** virus hominis 1 in CSF of some patients with very high titres in serum and probable lesions of the blood brain barrier.

8/7/8 (Item 5 from file: 73)
DIALOG(R)File 73:EMBASE

00689474 EMBASE No: 1977034810
Synergistic antiviral effects of adenine arabinoside and humoral antibodies in experimental **encephalitis** due to Herpesvirus hominis
Cho C.T.; Feng K.K.; Brahmacupta N.
Dept. Ped., Univ. Kansas Med. Cent., Coll. Hlth Sci., Kansas City, Kans. 66103 United States
Journal of Infectious Diseases (J. INFECT. DIS.) 1976, 133/2 (157-167)
CODEN: JIDIA
DOCUMENT TYPE: Journal
LANGUAGE: ENGLISH

The antiviral effects of humoral antibodies and adenine arabinoside on **encephalitis** due to Herpesvirus hominis were studied in three week old mice. Exogenously administered antibodies to H. hominis, of rabbit or human origin, significantly reduced morbidity and mortality rates from H. hominis **encephalitis** if enough antibodies were given during the early phase of infection. Adenine arabinoside could also modulate the pathogenesis and reduce the mortality rate in mice with H. hominis **encephalitis**. Simultaneous administration of adenine arabinoside and human immune globulin resulted in an enhanced protection against H. hominis **encephalitis**. This increased protection was manifested by a significant reduction of mortality rate, a decrease in concentration of virus, and a lessening of histopathologic damage in the brain tissues. Mechanisms involved in the enhanced protective effects were not well defined. The use of adenine arabinoside plus human immune globulin did not

completely suppress viral replication. Therefore, host recovery was probably mediated through partial **suppression** of viral replication by adenine arabinoside, neutralization of cell free virus by antibodies, and collaboration of antibodies with other host resistance factors (e.g., complement, **leukocytes**, nonimmune effector cells, etc.). Our data suggest that control of severe H. hominis infection may require the combined use of an antiviral agent and humoral factor and, perhaps, enhancement of host responses by other means.

8/7/9 (Item 6 from file: 73)
DIALOG(R)File 73:EMBASE

00254037 EMBASE No: 1975026300
Lead aggravates viral disease and represses the antiviral activity of interferon inducers
Gainer J.H.
Nat. Inst. Environm. Hlth Sci., Research Triangle Park, N.C. 27709
United States
Environmental Health Perspectives (ENVIRON. HEALTH PERSPECT.) 1974, No. 7/- (113-119)
CODEN: EVHPA
DOCUMENT TYPE: Journal
LANGUAGE: ENGLISH

Lead acetate was administered continuously in the drinking water to CD 1 male mice beginning at 4 weeks of age. An LD(10-20) of the lytic viruses or 300 plaque forming units of RLV was inoculated intraperitoneally at 6 weeks of age. Lead increased the response of the mice to all classes of viruses against which it was tested: an RNA picornavirus encephalomyocarditis (EMCV), a DNA herpesvirus pseudorabies, an RNA leukemia virus Rauscher leukemia (RLV), an RNA arbovirus B St. Louis **encephalitis**, and an RNA arbovirus A western **encephalitis**. Most studies were performed between lead and EMCV. Increases in EMCV mortality in lead treated mice over controls ranged from 2 x at a lead level of 0.004 M to 7 x (100% mortality) at a 0.1 M lead level. Splenomegaly with spleens 800 to 1100 mg in weight containing high titers of RLV occurred in lead (0.03 M) treated mice 3 and 6 weeks after RLV inoculation; spleens of RLV controls were normal in weight (200 mg) and were free of virus. Lead did not reduce the protective effect of mouse interferon (IF) against the lethal action of EMCV, but it did repress the EMCV antiviral effect of poly I/poly C (PIC) and of Newcastle disease virus (NDV) against EMCV mortality. These data indicate several new facts concerning adverse effects lead may have on an animal: lead aggravates viral disease, most likely in part, through reduced IF synthesis; lead represses the anti EMCV protective effects of both PIC and of NDV, which, in other reports, were shown to induce IF in radioresistant macrophages (PIC) or in radiosensitive **lymphocytes** (NDV); lead may then be said to repress IF induction in two kinds of cells; however, lead does not **inhibit** IF action.

8/7/10 (Item 1 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

08071362 95084672
[The immunomodulating and metabolic actions of thymalin in an experimental herpetic infection]
Immunomoduliruiushchee i metabolicheskoe deistvie timalina pri eksperimental'noi gerpeticheskoi infektsii.
Chukhlovina ML; Tsinzerling VA; Zalkind LG; Polushkina LI; Nilova LG; Mazing IuA; Kuz'min VO
Zh Mikrobiol Epidemiol Immunobiol (RUSSIA) Jul-Aug 1994, (4) p77-81, ISSN 0372-9311 Journal Code: Y9O
Languages: RUSSIAN Summary Languages: ENGLISH

Document type: JOURNAL ARTICLE English Abstract

In experiments on the intracerebral inoculation of **herpes** virus, type I, into 38 CBA mice the phagocytic activity of peritoneal exudate, cells, spontaneous migration of leukocytes and their response to phytohemagglutinin (PHA), the activity of key enzymes of gluconeogenesis, lipid peroxidation in liver tissue, as well as the level of glucose and glycosylated hemoglobin in the blood, were determined simultaneously with the histological study of the brain and the main internal organs of the animals, receiving thymalin treatment and not receiving it. As demonstrated in these experiments, the development of experimental infection was accompanied by the **inhibition** of the phagocytic activity of peritoneal macrophages and response of **leukocytes** to PHA, as well as metabolic shifts in liver tissue. Treatment with thymalin produced a combined immunomodulating and metabolic effect.

8/7/11 (Item 2 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

06021657 85236257

Protection from **herpes** simplex virus-induced neuropathology in mice showing delayed hypersensitivity tolerance.

Altmann DM; Blyth WA

J Gen Virol (ENGLAND) Jun 1985, 66 (Pt 6) p1297-303, ISSN 0022-1317 Journal Code: I9B

Languages: ENGLISH

Document type: JOURNAL ARTICLE

Herpes simplex virus (HSV)-susceptible mice inoculated under conditions favouring the preferential activation of T suppressor (Ts) cells acting on the delayed-type hypersensitivity (DTH) response to the virus were protected from lethal **herpes encephalitis** and from central nervous system (CNS) demyelination (as reflected by ear paralysis), compared to controls given normal priming. Thus, suppressed DTH was not incompatible with recovery from acute infection and may indeed have been beneficial. Protection could be transferred by T cells from donors given a 'DTH-tolerogenic' priming regime. It was unlikely that protection resulted from enhancement of other mechanisms such as cytotoxic T cell activation, antibody or interferon production, since no reduction of virus spread was observed in protected mice. In addition, several aspects of Ts cell activation by intravenous inoculation of avirulent HSV type 1 have been characterized. Suppression was virus dose-dependent and could be transferred to the efferent limb of a DTH response. Activation of Ts cells for DTH coincided with an enhanced antibody response. It is suggested that protection in this model may be mediated by Ts cells which act to limit DTH-mediated immunopathology in the CNS.

8/7/12 (Item 3 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

04499863 82253542

A recent overview on in vitro and in vivo immunological activities of methisoprinol.

Morin A; Ballet JJ

Allergol Immunopathol (Madr) (SPAIN) Mar-Apr 1982, 10 (2) p109-14, ISSN 0211-6448 Journal Code: 3AH

Languages: ENGLISH

Document type: JOURNAL ARTICLE; REVIEW

Methisoprinol (Isoprinosine), a purine derivative, has been shown to exert a number of immunopharmacological effects, both in vitro and in vivo, in animal and human studies. The agent, somehow mimicking the effects of thymic factors, induces the appearance of phenotypic markers of differentiation on immature precursor T cells; enhances the proliferative response of murine and human **lymphocytes** to mitogens or antigens,

augments helper or **suppressor** T cell functions and increases the production of lymphotoxin a lymphokine. It has also been shown that this drug can potentiate the effects of macrophage activating factor to stimulate macrophage, and of interferon to protect mice against experimental viral and tumor challenges. In humans, beneficial results have been reported from clinical trials testing the effects of methisoprinol in a variety of diseases including subacute sclerosing panencephalitis (SSPE), acute viral **encephalitis**, recurrent mucocutaneous infections due to type I and II **Herpes** viruses as well as in immune restoration of cancer patients with immunodepression following radiotherapy. The drug is also being studied in immunopathological disorders such as rheumatoid arthritis, systemic lupus erythematosus. Sjogren's disease and type A hepatitis. The large spectrum of effects of methisoprinol on a number of immune parameters, the increasing evidence of its therapeutic value in several pathological conditions and its safety of use qualifies this drug as an interesting immunoregulating agent. (34 Refs.)

8/7/13 (Item 4 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

04424153 85029221
Lipopolysaccharide-induced suppressor cells for delayed-type hypersensitivity to **herpes** simplex virus: nature of suppressor cell and effect on pathogenesis of **herpes** simplex.
Altmann DM; Blyth WA
Immunology (ENGLAND) Nov 1984, 53 (3) p473-80, ISSN 0019-2805
Journal Code: GH7
Languages: ENGLISH
Document type: JOURNAL ARTICLE
Treatment of mice with LPS at the time of priming with **herpes** simplex virus type 1 (HSV1) causes the preferential activation of virus-specific T suppressor (Ts) cells. These Ts cells can transfer suppression to the efferent limb of a DTH response. Priming under these conditions is associated with enhanced cell-recruitment to the inoculation site, but had no effect on virus clearance. The induction of suppression was abrogated by pretreatment of mice with cyclophosphamide or indomethacin. LPS had no effect on the antibody response to HSV1 during acute infection, although treated mice showed a raised antibody titre one month after inoculation. Susceptible mice inoculated with HSV1 and given LPS showed protection, both from lethal **herpes encephalitis** and from demyelination within the CNS as reflected by ear paralysis. These results imply that, during some stages of acute infection, T cell effector mechanisms may themselves mediate tissue damage. At such times, Ts cells may perform a beneficial role leading to a reduction in pathology.

8/7/14 (Item 1 from file: 357)
DIALOG(R)File 357:DERWENT BIOTECHNOLOGY ABS

0235913 DBA Accession No.: 99-06014 PATENT
New human reticulocalbin isoforms - expression in host cell, antibody, agonist and antagonist used for disease therapy
AUTHOR: Bandman O; Hillman J L; Lal P; Corley N C; Shah P
CORPORATE SOURCE: Palo Alto, CA, USA.
PATENT ASSIGNEE: Incyte-Pharm. 1999
PATENT NUMBER: WO 9907849 PATENT DATE: 990218 WPI ACCESSION NO.: 99-180492 (9915)
PRIORITY APPLIC. NO.: US 910927 APPLIC. DATE: 970808
NATIONAL APPLIC. NO.: WO 98US16259 APPLIC. DATE: 980805
LANGUAGE: English
ABSTRACT: A substantially purified human reticulocalbin-gamma (R1, 328 amino acids) and human reticulocalbin-delta (R2, 315 amino acids), are new. Also claimed are: a polynucleotide sequence encoding R1 or R2; a

polynucleotide sequence which hybridizes to or is complementary to the above polynucleotides; a polynucleotide sequence of 1,463 or 1,120 bp or complementary polynucleotide; an expression vector; a host cell; the production of a R1 or R2; and R1 or R2 specific antibodies, agonists and **antagonists** . R1 and R2 can be used to treat infectious or developmental disorders including pneumonia, **lymphocytic** choriomeningitis, Hanta virus, chronic bronchitis, hepatitis, **herpes** virus, yellow fever, influenza, cancer, measles, mumps, rhino virus, polio virus, coxsackie virus, smallpox, Colorado tick fever, HIV virus, rabies, gastroenteritis and rubella, **encephalitis** , and bacterial, fungal, parasitic, protozoal, helminthic infections, kidney tubular acidosis, anaemia, Cushing syndrome, achondroplastic dwarfism, epilepsy, etc. R1 and R2 antagonists can be used to treat cancer or immunological disorders. (53pp)

```
Set     Items   Description
S1        108   E1-E11
S2          8   S1 AND (VLA(W)4)
S3          5   RD S2 (unique items)
S4          1   VLA(W)4 AND HERPES
S5          2   VLA(W)4 AND ARBOVIRUS
S6          2   RD S5 (unique items)
S7          3   VLA(W)4 AND VIRAL(W)ENCEPHALITIS
S8          1   RD S7 (unique items)
? s vla(w)4 and (21(w)6)(30n)(antibod?)

Processing
            5509  VLA
         4522487  4
            3338  VLA(W)4
          764236  21
         3423440  6
         1526273  ANTIBOD?
             145  21(W)6(30N)ANTIBOD?
      S9       3  VLA(W)4 AND (21(W)6)(30N)(ANTIBOD?)
? rd s9

...completed examining records
     S10       1  RD S9 (unique items)
? t s10/7/all


 10/7/1     (Item 1 from file: 5)
DIALOG(R)File   5:Biosis Previews(R)
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08992782   BIOSIS NO.: 199497001152
VLA-4-dependent adhesion activities of U937 cells and
  guinea-pig bronchoalveolar lavage leukocytes.
AUTHOR: Monshizadegan D A(a); Holloway D A; Torrente J M; Yednock T; Fritz
  L; Sturm R J
AUTHOR ADDRESS: (a)Wyeth-Ayerst Res., CN 8000, Princeton, NJ 08543**USA
JOURNAL: Agents and Actions  39 (SPEC. CONF. ISSUE):pC177-C179 1993
ISSN: 0065-4299
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: VLA-4-dependent binding to fibronectin (FN) and to a
  human vascular cell adhesion molecule (hVCAM-1)-transfected murine cell
  line was measured using U937 cells and guinea pig (GP) bronchoalveolar
  lavage (BAL) cells. A species cross-reactive, blocking monoclonal
  antibody directed against human VLA-4 (TY 21.
  6) inhibited U937/FN binding by 71 + 7%. The presence of TY
  21.6 inhibited the stimulated binding of U937 cells to
  hVCAM-1 by 84%. However, TY 21.6 was unable to inhibit the BAL/FN
  binding. With the addition of TY 21.6, the binding of PMA-stimulated BAL
  cells to hVCAM-1 was inhibited by 57 +- 5%. In summary, human and
  guinea-pig leukocytes express binding activity to both FN and hVCAM-1. A
  specific VLA-4 blocking monoclonal antibody, TY
  21.6, inhibited U937 and BAL cell binding to hVCAM-1, but
  only inhibited FN binding with U937 cells.
```

s (vla(w)4)(30n)(antibod?) and (treat? or therap? or inhibit? or suppress? or antagoni?)(30n)(viral(w)encephalitis or encephalitis or herpes or arborvirus?)

Processing

425	VLA
2656699	4
39637	ANTIBOD?
59	VLA(W)4(30N)ANTIBOD?
616495	TREAT?
98780	THERAP?
288635	INHIBIT?
142635	SUPPRESS?
24693	ANTAGONI?
21642	VIRAL
1571	ENCEPHALITIS
65	VIRAL(W)ENCEPHALITIS
1571	ENCEPHALITIS
8097	HERPES
3	ARBORVIRUS?
3624	((((TREAT? OR THERAP?) OR INHIBIT?) OR SUPPRESS?) OR ANTAGONI?)(30N)(((VIRAL(W)ENCEPHALITIS OR ENCEPHALITIS) OR HERPES) OR ARBORVIRUS?)
S6 3	(VLA(W)4)(30N)(ANTIBOD?) AND (TREAT? OR THERAP? OR INHIBIT? OR SUPPRESS? OR ANTAGONI?)(30N)(VIRAL(W)ENCEPHALITIS OR ENCEPHALITIS OR HERPES OR ARBORVIRUS?)

? t s6/3/all

6/3/1 (Item 1 from file: 654)
DIALOG(R)File 654:US Pat.Full.

03055104

Utility
INHIBITORS OF LEUKOCYTE ADHESION

PATENT NO.: 6,001,809
ISSUED: December 14, 1999 (19991214)
INVENTOR(s): Thorsett, Eugene D., Moss Beach, CA (California), US (United States of America)
Yednock, Theodore A., Fairfax, CA (California), US (United States of America)
Pleiss, Michael A., Fremont, CA (California), US (United States of America)
ASSIGNEE(s): Elan Pharmaceuticals, Inc , (A U.S. Company or Corporation), South San Francisco, CA (California), US (United States of America)
APPL. NO.: 8-467,580
FILED: June 06, 1995 (19950606)

This application is a continuation-in-part of U.S. patent application Ser. No. 08-273,055 filed July 11, 1994, now abandoned, which application is incorporated herein by reference in its entirety.

FULL TEXT: 3429 lines

6/3/2 (Item 2 from file: 654)

DIALOG(R)File 654:US Pat.Full.
(c) format only 1999 The Dialog Corp. All rts. reserv.

03047334
Utility
ANTI-IGE ANTIBODIES AND METHODS OF IMPROVING POLYPEPTIDES

PATENT NO.: 5,994,511
ISSUED: November 30, 1999 (19991130)
INVENTOR(s): Lowman, Henry B., El Granada, CA (California), US (United States of America)
Presta, Leonard G., San Francisco, CA (California), US (United States of America)
Jardieu, Paula M., San Mateo, CA (California), US (United States of America)
Lowe, John, Daly City, CA (California), US (United States of America)
ASSIGNEE(s): Genentech, Inc , (A U.S. Company or Corporation), South San Francisco, CA (California), US (United States of America)
[Assignee Code(s): 7579]
APPL. NO.: 8-887,352
FILED: July 02, 1997 (19970702)
FULL TEXT: 5666 lines

6/3/3 (Item 3 from file: 654)
DIALOG(R)File 654:US Pat.Full.
(c) format only 1999 The Dialog Corp. All rts. reserv.

02612754
Utility
ANTISENSE OLIGONUCLEOTIDES DIRECTED AGAINST HUMAN VCAM-1 RNA
[Treatment of septic shock, adult respiratory distress syndrome]

PATENT NO.: 5,596,090
ISSUED: January 21, 1997 (19970121)
INVENTOR(s): Hoke, Glenn D., Mt. Airy, MD (Maryland), US (United States of America)
Bradley, Matthews O., Laytonsville, MD (Maryland), US (United States of America)
Williams, Taffy J., Lansdale, PA (Pennsylvania), US (United States of America)
Lee, Che-Hung, Silver Spring, MD (Maryland), US (United States of America)
ASSIGNEE(s): The United States of America as represented by the Secretary of the Navy, (A U.S. Government Agency), Washington, DC (District of Columbia, US (United States of America)
[Assignee Code(s): 86584]
EXTRA INFO: Assignment transaction [Reassigned], recorded June 10, 1997 (19970610)
APPL. NO.: 8-137,701
FILED: October 12, 1993 (19931012)

RELATED APPLICATION

This application is a Continuation-in-Part of application 07-918,256, filed 24 Jul. 1992, now abandoned.

FULL TEXT: 1247 lines
? t s6/k/all

6/K/1 (Item 1 from file: 654)
DIALOG(R)File 654:(c) format only 1999 The Dialog Corp. All rts. reserv.

... invention to promote adhesion of Jurkat cells in the presence and

absence of an anti-**VLA-4 antibody**.

FIG. 2 shows the results of experiments demonstrating the ability of peptides of the invention...
...adhesion signal sequences recognized by VLA-4. Thus, the peptides can be used to block **VLA-4** -mediated adhesion and inhibit immunopathologies associated with this adhesion.

The invention is based, in part, upon sequence analysis of 5 monoclonal **antibodies** against alpha 4 integrin that inhibit **VLA-4** binding to VCAM-1. This analysis revealed a short consensus stretch of amino acids within the heavy chain CDR3 of these **antibodies**. Three of the anti- alpha 4 **antibodies** contain YGN . . . Y, while the fourth contains FGN . . . Y, (Y is typically considered to be...The peptides of the invention thus comprise sequences derived from the sequences of the anti-**VLA-4 antibodies** noted above or from domains of VCAM-1. These sequences present adhesion signals which allow the peptides to inhibit **VLA-4** mediated adhesion in vivo, for instance by binding **VLA-4** thereby disrupting the binding of VLA-4 to VCAM-1. Preferred adhesion signal sequences are...The test compounds can also be tested for the ability to competitively inhibit binding between **VLA-4** and VCAM-1, or between **VLA-4** and a labelled compound known to bind **VLA-4**, such as peptides of the invention or **antibodies** to **VLA-4**. In these assays the VCAM-1 can be immobilized on a solid surface. Alternatively, VCAM...myocardial ischemia, and inflammatory bowel disease. In preferred embodiments the pharmaceutical compositions are used to **treat** inflammatory brain disorders, such as multiple sclerosis (MS), viral meningitis and **encephalitis**.

Pharmaceutical compositions of the invention are suitable for use in a variety of drug delivery...Jurkat Cells to Peptide-BSA Conjugates

This example demonstrates that a peptide derived from the **antibody** 21/6 CDR3 region interacts specifically with **VLA-4** integrin.

The peptide used in this example was synthesized based on the sequence of the anti- alpha sub 4 integrin **antibody** 21/6 (CGGEGYYGNYGVYA, SEQ ID No. 1). In this example the peptide was conjugated to VCAM-1

This example demonstrates that peptides derived from the **antibody** 21/6 CDR3 region can be used as competitive inhibitors of **VLA-4** integrin interaction with VCAM-1.

VCAM-1 was expressed as a soluble fusion protein. The...

... soluble construct with Jurkat cells was monitored by standard FACS analysis, using a fluorescently labeled **antibody** directed against the construct's human IgG tail as a marker.

The activity of **VLA-4** can be regulated. 15/7 is a monoclonal **antibody** that recognizes an activated conformation of **VLA-4** and locks the molecule in the active state, thereby enhancing **VLA-4** -mediated cell adhesion. 15/7 stabilizes the interaction of Jurkat cells with the soluble VCAM...

... and 15/7, the soluble VCAM-1 construct interacted with the cell surface in an **VLA-4** -dependent fashion; the interaction was inhibited completely by anti- alpha 4 integrin (21/6), but not by the IOT18 **antibody** against beta sub 2

6/K/2 (Item 2 from file: 654)

... proteins; homing receptors; adressins; regulatory proteins; integrins such as CD11a, CD11b, CD11c, CD18, and ICAM, **VLA-4** and VCAM; a

tumor associated antigen such as HER2, HER3 or HER 4 receptor; and fragments of any of the above-listed peptides.

Preferred molecular targets for **antibodies** encompassed by the present invention include CD proteins such as CD3, CD4, CD8, CD19, CD20 receptor; cell adhesion molecules such as LFA-1, Mac12, p150,95, **VLA-4** , ICAM-1, VCAM and alpha v/ beta 3 integrin including either a orb subunits thereof (e.g. anti-CD11a, anti-CD18 or anti-CD11b **antibodies**); growth factors such as VEGF; IgE; blood group antigens; flk2/flk3 receptor; obesity (OB) receptor...g. Fc gamma RI, Fc gamma RII or Fc gamma RIII); BsAbs for use in **therapy** of infectious diseases such as anti-CD3-anti-**herpes** simplex virus (HSV), anti-T-cell receptor: CD3 complex/anti-influenza, anti-Fc gamma R...

6/K/3 (Item 3 from file: 654)

... unstimulated or activated endothelium by disruption of the recognition that occurs between VCAM-1 and **VLA-4**. The use of monoclonal **antibodies** against either **VLA-4** and/or VCAM-1 can be useful in preventing the recognition of the receptor/ligand...in vivo data has shown that antisense oligonucleotides to 5' viral sequences of tick-borne **encephalitis** virus were capable of providing protection (30-50% survival in **treated** animals versus 100% lethality for control mice receiving no antisense oligonucleotide) in mice from viral...

```
Set     Items   Description
S1       6758   (HERPES OR HSV?) AND ENCEPHALITIS
S2        170   S1 AND (MULTIPLE(W)SCLEROSIS)
S3         13   S2 AND REVIEW?
S4         12   RD S3 (unique items)
? s s1 and py=1995

            6758  S1
         1959822  PY=1995
      S5     272  S1 AND PY=1995
? s s5 and hse

             272  S5
            1856  HSE
      S6      19  S5 AND HSE
? rd s6

...completed examining records
      S7       9  RD S6 (unique items)
? t s7/7/all


 7/7/1     (Item 1 from file: 5)
DIALOG(R)File   5:BIOSIS PREVIEWS(R)
(c) 1999 BIOSIS. All rts. reserv.

10140464   BIOSIS NO.: 199698595382
Mild form of acute herpes simplex encephalitis in childhood.
AUTHOR: Marton Revital; Gotlieb-Stematsky Tamar; Klein Colin; Lahat Eli;
  Arlazoroff Aharon(a)
AUTHOR ADDRESS: (a)Dep. Neurol., Assaf Harofeh Med. Cent., Zerifin 70300**
  Israel
JOURNAL: Brain & Development  17 (5):p360-361 1995
ISSN: 0387-7604
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: We describe two patients, aged 3.5 years and 15 years, with a
  mild form of herpes simplex encephalitis (HSE). The
  disease was characterized by convulsions and lymphocytic pleocytosis in
  the cerebrospinal fluid (CSF). Involvement of herpes simplex virus
  (HSV) was established by antibody measurements in serum and CSF.
  Recovery was complete with no antiviral drug administration. It appears
  that scrutinized serological work-up would widen our concept of mild
  forms of HSE, with a better prognosis and complete recovery.


 7/7/2     (Item 2 from file: 5)
DIALOG(R)File   5:BIOSIS PREVIEWS(R)
(c) 1999 BIOSIS. All rts. reserv.

09968801   BIOSIS NO.: 199598423719
Small amounts of exogenous IL-4 increase the severity of encephalitis
  induced in mice by the intranasal infection of herpes simplex virus
  type 1.
AUTHOR: Ikemoto Kaori; Pollard Richard B; Fukumoto Tetsuo; Morimatsu
  Mitsunori; Suzuki Fujio(a)
AUTHOR ADDRESS: (a)Dep. Internal Med., Univ. Texas Med. Branch, 301
```

University Blvd., Galveston, TX 77555-0882**USA
JOURNAL: Journal of Immunology 155 (3):p1326-1333 1995
ISSN: 0022-1767
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: The effect of murine rIL-4 on the development of herpesvirus **encephalitis** (**HSE**) in mice infected intranasally with **herpes** simplex virus type 1 (**HSV**-1) was investigated. The mortality rates of mice infected with a 0.5 LD-50 dose of **HSV**-1 were greatly increased after the administration of rIL-4 at doses ranging from 0.01 to 1.0 U/mouse 2 h before and 2, 4, and 6 days after the infection. In contrast, survival rates of mice exposed to a 5 LD-50 dose of **HSV**-1 were clearly increased when these mice were treated with anti-IL-4 mAb. Cervical lymph node (CLN) cells and cerebrospinal fluid (CSF) cells from mice with **HSE** (**HSE** mice) produced IL-4 in their culture fluids when they were stimulated in vitro with **HSV**-1 Ag. Increased amounts of **HSV**-1 infection in mice resulted in the increased production of IL-4 in the culture fluids of local lymphocytes. However, significant amounts of IL-4 were not produced in serum specimens or in culture fluids of spleen cells from **HSE** mice. IL-4 production in culture fluids of CLN and CSF cells from **HSE** mice was clearly reduced after treatment of **HSE** mice with anti-IL-4 mAb. Furthermore, IL-4 production by CLN and CSF cells was greatly enhanced when the cells were prepared from **HSE** mice previously treated with rIL-4. The IL-4 was mainly produced from CD4+ T cells. These results demonstrate that small amounts of exogenous IL-4 increase the severity of **HSE** in **HSV**-1-infected mice through the increased production of IL-4 from local CD4+ T cells.

7/7/3 (Item 3 from file: 5)
DIALOG(R)File 5:BIOSIS PREVIEWS(R)

09953679 BIOSIS NO.: 199598408597
Spatial recognition memory deficits without notable CNS pathology in rats following **herpes** simplex **encephalitis**.
AUTHOR: Beers David R; Henkel Jenny S; Kesner Raymond P; Stroop William G (a)
AUTHOR ADDRESS: (a)Dep. Microbiol. Immunol., Univ. Arkansas Med. Sci., 4301 West Markham, Mail Slot 511, Little Roc**USA
JOURNAL: Journal of the Neurological Sciences 131 (2):p119-127 1995
ISSN: 0022-510X
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: Survivors of **herpes** simplex **encephalitis** (**HSE**) experience intellectual impairment and an inability to store and recall information. Because the temporal lobes and associated limbic structures are central to storage and retrieval of memories, and are predominantly affected in adult **HSE**, injury to these areas is postulated to cause behavioral and learning disabilities. A previous study (Beers et al., 1993) demonstrated that intranasal inoculation of Lewis rats with **herpes** simplex virus type-1 (**HSV**-1) induced acute partial complex seizures, and hemorrhagic and inflammatory lesions of the hippocampus and entorhinal cortex. Consequently, it was of interest to determine whether rats that had recovered from **HSE** had limbic system-associated memory impairments. Therefore, rats were evaluated when signs and symptoms of **encephalitis** were no longer apparent using an eight arm radial maze to assess the acquisition and retention of learned information. An allocentric-spatial location paradigm revealed **HSV** -1 infected rats performed at chance levels on both acquisition and retention which were statistically different from sham-inoculated

controls. However, using an egocentric-spatial left/right discrimination task, infected rats performed statistically similar to sham-inoculated controls. Furthermore, **HSV**-1 nucleic acids were detected in the nuclei of neurons within the hippocampus and entorhinal cortex using in situ hybridization techniques. Of interest was the observation that rats with learning and memory deficits had no apparent histopathological or immunocytochemical evidence of antecedent CNS infection. This is the first experimental demonstration that **HSV**-1 can cause behavioral impairments in the absence of obvious inflammatory injury to the temporal lobe memory system.

7/7/4 (Item 4 from file: 5)
DIALOG(R)File 5:BIOSIS PREVIEWS(R)

09869964 BIOSIS NO.: 199598324882
Hyperfixation of 99mTc-HMPAO and hypofixation of 123I-iomazenil in acute **herpes encephalitis**.
AUTHOR: Launes Jyrki(a); Hokkanen Laura; Nikkinen Paivi; Liewendahl Kristian; Salonen Oili; Siren Jan; Livanianen Matti
AUTHOR ADDRESS: (a)Dep. Neurol., Lab., Univ. Central Hosp., Haartmaninkatu 4, SF-00290 Helinki**Finland
JOURNAL: Neuroreport 6 (8):p1203-1206 1995
ISSN: 0959-4965
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: We studied two patients with **herpes encephalitis** (**HSE**) by (99mTc)HMPAO and (123I)iomazenil single photon emission computed tomography. Increased uptake of HMPAO was seen for up to 63 days in the **HSE** affected brain area. Iomazenil binds to benzodiazepine receptors and can measure neurone loss. Decreased iomazenil uptake was observed a few days after onset, at a time when hyperfixation of HMPAO occurred. Because in **HSE** neurone loss occurs simultaneously with hyperfixation of HMPAO, it is unlikely that this hyperfixation is caused by increased neuronal activity, as in epilepsy. This suggests that the hyperfixation of HMPAO in **HSE** occurs in glia and is sustained by inflammation-related hypermetabolism and acidity. The early neurone loss in **HSE** stresses the importance of immediate antiviral treatment.

7/7/5 (Item 5 from file: 5)
DIALOG(R)File 5:BIOSIS PREVIEWS(R)

09782146 BIOSIS NO.: 199598237064
Diagnosis of **herpes** simplex **encephalitis**: Application of polymerase chain reaction to cerebrospinal fluid from brain-biopsied patients and correlation with disease.
AUTHOR: Lakeman Fred D(a); Whitley Richard J; Group The National Institute Of Allergy And Infectious Diseases Collaborative Antiviral Study
AUTHOR ADDRESS: (a)Dep. Pediatr. Microbiol. and Med., Univ. Alabama at Birmingham, 309 BBRB, 845 19th St. S. UAB St**USA
JOURNAL: Journal of Infectious Diseases 171 (4):p857-863 1995
ISSN: 0022-1899
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: Isolation of **herpes** simplex virus (**HSV**) from brain tissue after biopsy has been considered the reference standard for the diagnosis of **herpes** simplex **encephalitis** (**HSE**). During the evaluation of antiviral treatment of **HSE**, cerebrospinal fluid (CSF) was obtained from patients with clinical disease indicative of

HSE who underwent diagnostic brain biopsy. **HSV** DNA was detected by polymerase chain reaction (PCR) in CSF of 53 (98%) of 54 patients with biopsy-proven **HSE** and was detected in all 18 CSF specimens obtained before brain biopsy from patients with proven **HSE**. Four of 19 CSF specimens were positive after 2 weeks of antiviral therapy. Positive results were found in 3 (6%) of 47 patients whose brain tissue was culture-negative. Detection of **HSV** DNA in the CSF correlated significantly with age and focal radiographic findings. Thus, PCR detection of **HSV** DNA should be the standard for diagnosis of **HSE**.

7/7/6 (Item 1 from file: 73)
DIALOG(R)File 73:EMBASE

06421517 EMBASE No: 1996074370
Brain irradiation and antioedematous dexamethasone treatment - Risk factors for **herpes** simplex **encephalitis**?
Dragoje S.; Tolnay M.; Dalquen P.; Probst A.
Institute of Pathology, Division of Neuropathology, Schonbeinstrasse 40,CH-4003 Basel Switzerland
Schweizer Archiv fur Neurologie und Psychiatrie (SCHWEIZ. ARCH. NEUROL. PSYCHIATR.) (Switzerland) 1995, 146/6 (277-280)
CODEN: SANPE ISSN: 0258-7661
DOCUMENT TYPE: Journal; Article
LANGUAGE: ENGLISH SUMMARY LANGUAGE: ENGLISH

Herpes simplex **encephalitis** (**HSE**) could result from the reactivation of an endogenous latent **herpes** simplex virus (**HSV**) in sensory ganglia or in brain parenchyma. Virus replication and a new lytic virus cycle may be triggered by a wide variety of factors. One of these might be irradiation as suggested by experimental evidence obtained in mouse trigeminal ganglia. Here we report the occurrence of **HSE** in a 52 years old woman two months after brain irradiation (40 Gray in 20 fractions) and dexamethasone administration for a metastatic brain tumor. **HSE** has already been observed in a clinical context very similar to that reported here, suggesting that brain irradiation together with corticoid therapy may, in some rare patients, favour the occurence of **HSV** reactivation and **HSE**.

7/7/7 (Item 2 from file: 73)
DIALOG(R)File 73:EMBASE

06288150 EMBASE No: 1995315635
A case of **herpes** simplex **encephalitis** recovered from comatous state
Nakasono M.; Tamura Y.; Yui Y.; Iwano K.; Ishida T.; Oda S.; Tezuka K.; Tsuda M.; Matsuoka M.; Iwamoto M.; Murakami T.; Gyouten T.; Ueda H.
Department of Internal Medicine, Zentsuji National Hospital, 2-1-1 Senyu-cho,Zentsuji, Kagawa 765 Japan
IRYO - Japanese Journal of National Medical Services (IRYO JPN. J. NATL. MED. SERV.) (Japan) 1995, 49/9 (777-781)
CODEN: IRYOA ISSN: 0021-1699
DOCUMENT TYPE: Journal; Article
LANGUAGE: JAPANESE SUMMARY LANGUAGE: JAPANESE; ENGLISH

Herpes simplex **encephalitis** (**HSE**) remains the serious secondary disease. The prognosis is correlated to the level of consciousness, age and the duration of illness. We reported a case of **HSE** in a 23-year-old female, who developed influenza-like symptoms first and fell into a coma with respiratory arrest 3 days later. Unexpectedly she recovered from the illness with the administration of vidarabine and acyclovir. In this case, we thought that the administration

of antiviral drugs at the early stage resulted in the recovery without leaving serious disability. It is often difficult to diagnose **HSE** at the early stage of the disease. From our experience, we suggest that when we suspect **HSE**, the early medication of the antiviral drugs is necessary.

7/7/8 (Item 3 from file: 73)
DIALOG(R)File 73:EMBASE

06148956 EMBASE No: 1995170723
Hyperfixation of sup 9sup 9sup mTc-HMPAO and hypofixation of sup 1sup 2sup 3I-iomazenil in acute **herpes encephalitis**
Launes J.; Hokkanen L.; Nikkinen P.; Liewendahl K.; Salonen O.; Siren J.; Iivanainen M.
Department of Neurology, Laboratory Department, University Central Hospital, Haartmaninkatu 4,SF-00290 Helsinki Finland
NeuroReport (NEUROREPORT) (United Kingdom) 1995, 6/8 (1203-1206)
CODEN: NERPE ISSN: 0959-4965
DOCUMENT TYPE: Journal; Article
LANGUAGE: ENGLISH SUMMARY LANGUAGE: ENGLISH

We studied two patients with **herpes encephalitis** (**HSE**) by (sup 9sup 9sup mTc)HMPAO and (sup 1sup 2sup 3I)iomazenil single photon emission computed tomography. Increased uptake of HMPAO was seen for up to 63 days in the **HSE** affected brain area. Iomazenil binds to benzodiazepine receptors and can measure neurone loss. Decreased iomazenil uptake was observed a few days after onset, at a time when hyperfixation of HMPAO occurred. Because in **HSE** neurone loss occurs simultaneously with hyperfixation of HMPAO, it is unlikely that this hyperfixation is caused by increased neuronal activity, as in epilepsy. This suggests that the hyperfixation of HMPAO in **HSE** occurs in glia and is sustained by inflammation-related hypermetabolism and acidity. The early neurone loss in **HSE** stresses the importance of immediate antiviral treatment.

7/7/9 (Item 1 from file: 399)
DIALOG(R)File 399:CA SEARCH(R)

124166455 CA: 124(13)166455f CONFERENCE PROCEEDING
PCR detection of HSV in cerebrospinal fluid
AUTHOR(S): Boerman, R. H.; Arnoldus, E. P. J.; Peters, A. C. B.; Van Loon, A. M.; Bloem, B. R.; Raap, A. K.
LOCATION: Department Neurology, Catholic University Hospital, Nijmegen, Neth.
JOURNAL: PCR: Protoc. Diagn. Hum. Anim. Virus Dis. EDITOR: Becker, Yechiel (Ed), Darai, Gholamreza (Ed), DATE: 1995 PAGES: 185-93 CODEN: 62DKAX LANGUAGE: English PUBLISHER: Springer,Berlin, Germany
SECTION:
CA203001 Biochemical Genetics
CA210XXX MICROBIAL, ALGAL, AND FUNGAL BIOCHEMISTRY
CA214XXX Mammalian Pathological Biochemistry
IDENTIFIERS: encephalitis detection HSV cerebrospinal fluid method, PCR detection method herpes simplex virus
DESCRIPTORS:
Encephalitis...
HSE; PCR detection of HSV in cerebrospinal fluid
Cerebrospinal fluid... Polymerase chain reaction... Virus,animal, herpes simplex...
PCR detection of HSV in cerebrospinal fluid

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Set     Items   Description
S1       6758   (HERPES OR HSV?) AND ENCEPHALITIS
S2        170   S1 AND (MULTIPLE(W)SCLEROSIS)
S3         13   S2 AND REVIEW?
S4         12   RD S3 (unique items)
S5        272   S1 AND PY=1995
S6         19   S5 AND HSE
S7          9   RD S6 (unique items)
? s s1 and py=1996

            6758  S1
         2049631  PY=1996
      S8     303  S1 AND PY=1996
? s s8 and hse

             303  S8
            1856  HSE
      S9      31  S8 AND HSE
? rd s9

...completed examining records
     S10      14  RD S9 (unique items)
? t s10/7/all


 10/7/1     (Item 1 from file: 5)
DIALOG(R)File   5:BIOSIS PREVIEWS(R)
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11479259   BIOSIS NO.: 199800260591
Magnetic resonance imaging of herpes simplex virus encephalitis
  : Reversible asymmetric basal ganglia lesions.
AUTHOR: Yoshii Fumihito(a); Akiyama Katsunori; Shinohara Yukito
AUTHOR ADDRESS: (a)Dep. Neurology, Tokai Univ. Sch. Med., Bohseidai,
  Isehara 259-11**Japan
JOURNAL: Internal Medicine (Tokyo)  35 (11):p909-911 Nov., 1996
ISSN: 0918-2918
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: We report a patient with herpes simplex virus type I
  encephalitis (HSE) who showed abnormal magnetic resonance
  imaging (MRI) signals in the basal ganglia. The lesions were asymmetric
  and became apparent with relapse of the neurological symptoms, but they
  completely disappeared, concomitantly with improvement of the illness.


 10/7/2     (Item 2 from file: 5)
DIALOG(R)File   5:BIOSIS PREVIEWS(R)
(c) 1999 BIOSIS. All rts. reserv.

10699509   BIOSIS NO.: 199799320654
Unusual course of herpes simplex virus encephalitis after
  acyclovir therapy.
AUTHOR: Preiser W; Weber B(a); Kloes G; Fischer P A; Doerr H W
AUTHOR ADDRESS: (a)Laboratoire Lieners et Hastert, rue de l'Hopital, L-9244
  Diekirch, Luxembourg**Germany
JOURNAL: Infection  24 (5):p384-389 1996
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ISSN: 0300-8126
RECORD TYPE: Abstract
LANGUAGE: English
SUMMARY LANGUAGE: English; German

ABSTRACT: This is a report on a case of **herpes** simplex **encephalitis** (**HSE**) taking an unusual course after initially successful acyclovir therapy. The etiology of **HSE** was proven serologically, by repeated detection of **herpes** simplex virus (**HSV**)-specific DNA sequences in cerebrospinal fluid (CSF) with polymerase chain reaction (PCR) and was supported by cerebral imaging. After both the neurological symptoms and laboratory findings had improved initially under acyclovir therapy, the patient's clinical condition deteriorated accompanied by a renewed increase in CSF pleocytosis and protein content. Nuclear magnetic resonance (NMR) imaging confirmed the finding of bilateral, mainly temporal lesions compatible with a diagnosis of relapsing **HSE**. The patient responded well to a second cycle of antiviral therapy but required a third treatment cycle due to renewed deterioration later on. **HSV**-specific DNA sequences could not be demonstrated in several consecutive CSF samples taken after the first week of illness but increased inflammatory changes typical of **HSE** were seen on NMR during phases of deterioration. IgM-class antibodies against **HSV** were detected in CSF 4 weeks after onset of symptoms and stayed positive for at least 7 weeks. Reasons for the repeated deterioration and possible explanations for the absence of **HSV** DNA in spite of what could be seen as relapses are discussed.

10/7/3 (Item 3 from file: 5)
DIALOG(R)File 5:BIOSIS PREVIEWS(R)

10640564 BIOSIS NO.: 199699261709
The role of laboratory investigation in the diagnosis and management of patients with suspected **herpes** simplex **encephalitis**: A consensus report.
AUTHOR: Cinque P; Cleator G M(a); Weber T; Monteyne P; Sindic C J; Van Loon A M
AUTHOR ADDRESS: (a)Dep. Pathological Sci., Div. Virol., Clinical Sci. Build., Manchester Royal Infirmary, Oxford Ro**UK
JOURNAL: Journal of Neurology Neurosurgery and Psychiatry 61 (4):p339-345 1996
ISSN: 0022-3050
DOCUMENT TYPE: Literature Review
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: As effective therapies for the treatment of **herpes** simplex **encephalitis** (**HSE**) have become available, the virology laboratory has acquired a role of primary importance in the early diagnosis and clinical management of this condition. Several studies have shown that the polymerase chain reaction (PCR) of CSF for the detection of **herpes** simplex virus type 1 (**HSV**-1) or type 2 (**HSV**-2) DNA provides a reliable method for determining an aetiological diagnosis of **HSE**. The use of PCR in combination with the detection of a specific intrathecal antibody response to **HSV** currently represents the most reliable strategy for the diagnosis and monitoring of the treatment of adult patients with **HSE**. The use of these techniques has also led to the identification of atypical presentations of **HSV** infections of the nervous system and permits the investigation of patients who develop a relapse of encephalitic illness after an initial episode of **HSE**. A strategy for the optimal use of the investigative laboratory in the diagnosis of **HSE** and subsequent management decisions is described.

10/7/4 (Item 4 from file: 5)
DIALOG(R)File 5:BIOSIS PREVIEWS(R)

10421804 BIOSIS NO.: 199699042949
Naming deficit in **herpes** simplex **encephalitis**.
AUTHOR: Barbarotto R; Capitani E(a); Laiacona M
AUTHOR ADDRESS: (a)Clin. Neurol. Ospedale San Paolo, Via Di Rudini 8, 20142 Milano**Italy
JOURNAL: Acta Neurologica Scandinavica 93 (4):p272-280 1996
ISSN: 0001-6314
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: Objectives - The preferential involvement of living categories in naming impairment is well recognized in **Herpes** Simplex **Encephalitis** (**HSE**). In this paper we describe naming, neuropsychological and neuroradiological findings with seven fresh **HSE** cases. Material & methods - Patients were given a picture naming task that included 60 items belonging to 6 different categories (three living, i.e. fruits, vegetables and animals and three nonliving, i.e. furniture, vehicles and tools). In the statistical analysis several possible sources of bias as the frequency of the target word, the familiarity with the objects to name, the image complexity and other parameters were taken into account. Results - Four out of seven patients were significantly more impaired with living things. We describe their general cognitive profile and discuss the anatomo-functional aspects of category dissociation. Conclusion - Language impairment, disproportionately severe for the naming of living exemplars, is frequently observed in **HSE**, is clinically relevant and should be specifically investigated.

10/7/5 (Item 5 from file: 5)
DIALOG(R)File 5:BIOSIS PREVIEWS(R)

10386678 BIOSIS NO.: 199699007823
Herpes simplex **encephalitis**.
AUTHOR: Skoldenberg Birgit
AUTHOR ADDRESS: Dep. Infect. Dis., Karolinska Inst., Danderyd Hosp., S-182 88 Danderyd**Sweden
JOURNAL: Scandinavian Journal of Infectious Diseases Supplementum 0 (100): p8-13 1996
ISSN: 0300-8878
DOCUMENT TYPE: Literature Review
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: **Herpes** simplex **encephalitis** (**HSE**) is a life-threatening condition with high mortality as well as significant morbidity in survivors. In most cases **herpes** simplex virus type 1 (**HSV**-1) is responsible for the diseases, however, the type 2 virus (**HSV**-2) is involved in 4-6% of cases. Primary **HSV** infection is identified in only one-third of patients with **HSE**. The majority of cases are recorded in adults with recurrent **HSV** infection who are already seropositive for **HSV** at the onset of symptoms, but only 6-10% of these patients have a history of labial **herpes**. Acute focal, necrotizing **encephalitis** with inflammation and swelling of the brain tissue are consistent features of the pathology of **HSE**. **HSV**-induced cytolysis certainly damages neurones, oligodendrocytes and astrocytes, but the role of cellular and humoral immunopathology is important. A complex network of cytokines seems to be active in regulating the local immune response and inflammation during and after **HSE**. Brain biopsy, serological analysis of intrathecal **HSV**

antibodies and detection of **HSV**-DNA in the cerebrospinal fluid (CSF) are all useful techniques to confirm the aetiology of **HSE**. Neurodiagnostic tests which support a presumptive diagnosis of **HSE** include: CSF analysis, electroencephalography, computer-assisted tomography and magnetic resonance imaging. Although acyclovir is the treatment of choice in **HSE**, mortality and morbidity still remain problematic. Long-term follow-up indicates that intrathecal cellular and humoral activation persist in **HSE**.

10/7/6 (Item 6 from file: 5)
DIALOG(R)File 5:BIOSIS PREVIEWS(R)

10371221 BIOSIS NO.: 199698826139
Acute **herpes** simplex **encephalitis**: Clinical assessment and prognostic data.
AUTHOR: Marton R; Gotlieb-Steimatsky T; Klein C; Arlazoroff A
AUTHOR ADDRESS: Dep. Neurol., Assaf Harofeh Med. Cent., Zerifin 70300** Israel
JOURNAL: Acta Neurologica Scandinavica 93 (2-3):p149-155 1996
ISSN: 0001-6314
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: Acute **herpes** simplex **encephalitis** (**HSE**) has a grave outcome, and detection of prognostic features is of clinical importance. Thirty patients with **HSE** were assessed in a retrospective study. Diagnosis was confirmed by serological methods using the indirect immunofluorescence technique (IFT). Antiviral treatment was given to 23 of the patients. Focal convulsions were more frequent in patients below 18 years of age, while confusion and memory disturbances were prevalent among patients above 18. The final outcome was influenced by the degree of severity of the disease at the peak and the state of consciousness and duration of disease prior to the initiation of anti-viral treatment. No correlation was found between antibody levels in serum or in CSF and the outcome. We conclude that the clinical degree of severity the duration of illness prior to treatment and state of consciousness at the initiation of anti-viral treatment are of prognostic importance.

10/7/7 (Item 7 from file: 5)
DIALOG(R)File 5:BIOSIS PREVIEWS(R)

10242543 BIOSIS NO.: 199698697461
Polymerase chain reaction in the investigation of "relapse" following **herpes** simplex **encephalitis**.
AUTHOR: Dennett C; Klapper P E(a); Cleator G M
AUTHOR ADDRESS: (a)Div. Virol., Dep. Pathol. Sci., Univ. Manchester, 3rd fl., Clin. Sci. Build., Manchester Royal I**UK
JOURNAL: Journal of Medical Virology 48 (2):p129-132 1996
ISSN: 0146-6615
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: Five cases of apparent relapse of **herpes encephalitis** were investigated. All patients recovered after antiviral and corticosteroid therapy. Samples of CSF taken from the patients at intervals through the initial and subsequent encephalitic episode were examined. PCR amplification of a 351 bp sequence from the Herpesvirus simplex (**HSV**) thymidine kinase gene demonstrated the presence of **HSV** DNA in CSF taken during the initial encephalitic illness but

not during the second encephalitic episode. Intrathecal synthesis of **HSV** antibody (**HSV** antibody index gt 1.9) was observed in all cases following the first episode, and there appeared to be no significant increase in intrathecal antibody synthesis in the second episode. High levels of CSF myelin basic protein were found during the acute phases of both the initial and the subsequent encephalitic illnesses. These data suggest that at least in our series of five patients, relapse following **HSE** may not be due to active viral replication.

10/7/8 (Item 1 from file: 73)
DIALOG(R)File 73:EMBASE

06776225 EMBASE No: 1997057719
Molecular diagnosis of **herpes** simplex **encephalitis**
Revello M.G.; Manservigi R.
Prof. R. Manservigi, Interdepartment Center Biotechnology, University of Ferrara, Via Fossato di Mortara 64b, I-44100 Ferrara Italy
Intervirology (INTERVIROLOGY) (Switzerland) 1996, 39/3 (185-192)
CODEN: IVRYA ISSN: 0300-5526
DOCUMENT TYPE: Journal; Review
LANGUAGE: ENGLISH SUMMARY LANGUAGE: ENGLISH
NUMBER OF REFERENCES: 69

Herpes simplex virus **encephalitis** (**HSE**) is associated with significant morbidity and mortality both in neonates and adults. An early diagnosis can greatly help to reduce mortality in both groups; however, since none of the presenting symptoms is pathognomonic for **HSE**, a clinical diagnosis is unreliable. On the other hand, the technique of isolating **herpes** simplex virus (**HSV**) from brain biopsies, although providing an early and specific diagnosis, has never been widely accepted because of the risk of neurological complications connected with the invasiveness of the method. In addition, several studies reported that the two **HSV** types appear to be differently associated with specific neurological complications, indicating that it would be important to gain a differential-type diagnosis to guide both prevention strategies and antiviral therapy. Therefore, the need for noninvasive specific and sensitive techniques has given impulse to the development of assays based on the search of either specific anti-**HSV** antibodies or viral DNA footprints in patient serum or cerebrospinal fluid. While enzyme-linked immunosorbent assays and immunoblot assays, using **HSV** type-1- and 2-specific viral glycoproteins, are useful for serological typing, the polymerase chain reaction technique has proved highly effective in giving early, precise and specific **HSE** diagnosis, thus providing a helpful tool for the identification and treatment of this disease.

10/7/9 (Item 2 from file: 73)
DIALOG(R)File 73:EMBASE

06712556 EMBASE No: 1996377512
Herpes simplex virus-1 infections in the normal and immunocompromised host
Skoldenberg B.
Department of Medicine, Karolinska Institute,S-182 88 Danderyd Sweden
Bailliere's Clinical Infectious Diseases (BAILLIERE'S CLIN. INFECT. DIS.) (United Kingdom) 1996, 3/3 (373-389)
CODEN: BCIDF ISSN: 1071-6564
DOCUMENT TYPE: Journal; Review
LANGUAGE: ENGLISH SUMMARY LANGUAGE: ENGLISH

The clinical manifestations and course of **HSV** infections depend on the anatomical site of the infection, the age and immune status of the host

and on whether the infection is primary or recurrent. Primary **HSV**-1 infections usually occur in young children; acute gingivostomatitis is the most frequent clinical manifestation. Primary **HSV**-1 infection is often asymptomatic and recurrent oral-facial **HSV** infection may be asymptomatic as well. The largest reservoir of **HSV** infections in the community is associated with recurrent labial **herpes**. **HSV** infection of the eye is the most common cause of corneal blindness in non-tropical areas. Primary herpetic keratoconjunctivitis is associated with unilateral or bilateral conjunctivitis. Recurrent **herpes** infection of the cornea may cause a spectrum of diseases. **HSV** infections are known to complicate several dermatological disorders, including atopic eczema, pemphigus and ichthyosis. **Herpes** simplex **encephalitis** (**HSE**) is a life-threatening disease with high mortality as well as significant morbidity in the survivors. In long-term follow-up of 37 patients (median 8.7 years), relapse of **HSE** was suspected in 10 episodes in six patients. In 11 of 14 (79%) patients with Bell's palsy, **HSV**-1 DNA was detected by PCR in endoneurial fluid and posterior auricular muscle but not in corresponding material from nine patients with Ramsay-Hunt syndrome. With severe immunosuppression, localized oral or cutaneous herpetic lesions may occur that fail to heal, become larger and form deeper and necrotic lesions. Acute fulminant or aggressive **HSV** infections can disseminate and cause oesophagitis, pneumonitis and/or hepatitis. As to aetiological diagnosis, **HSV** is easy to cultivate by tissue culture techniques; however, demonstration of **HSV** antigen or viral DNA by PCR or type-specific **HSV** antibodies might be more appropriate in the individual case.

10/7/10 (Item 3 from file: 73)
DIALOG(R)File 73:EMBASE

06691417 EMBASE No: 1996356351
Proton MR spectroscopy findings in **herpes** simplex **encephalitis**
Hitosugi M.; Ichijo M.; Matsuoka Y.; Takenaka N.; Fujii H.
Department of Internal Medicine, Kawasaki Municipal Hospital,Kawasaki Japan
Clinical Neurology (CLIN. NEUROL.) (Japan) 1996, 36/7 (839-843)
CODEN: RISHD ISSN: 0009-918X
DOCUMENT TYPE: Journal; Article
LANGUAGE: JAPANESE SUMMARY LANGUAGE: ENGLISH; JAPANESE

Localized proton magnetic resonance spectroscopy (sup 1H-MRS) was conducted in two patients with **herpes** simplex virus type I **encephalitis** (**HSE**). MR spectra of bilateral temporal lobes were acquired by the single voxel method using 1.5T unit. Peaks indicating N-acetyl asparate (NAA), choline (Cho) and creatine including phosphocreatine (Cr) wree identified and ratios of NAA/Cr and Cho/Cr were calculated. These ratios were compared with those of the contralateral side showing normal MRI findings and also with the control spectra obtained from normal volunteers. Three abnormal findings were observed in the spectra of the patients suffering from **HSE**; (1) significant reduction of the NAA/Cr ratio at the involved temporal lobe, (2) mild reduction of the NAA/Cr ratio at the normal temporal lobe, and (3) elevation of the Cho/Cr ratio at the bilateral lobes, but more significant on the involved sides. These results indicated that neural loss and gliosis occurred in the contralateral area with normal MR images as well as the involved hemisphere. We concluded that sup 1H-MRS is able to show the specific histological findings of **herpes** simplex **encephalitis**. This is the first report assessing sup 1H-MRS for patients with **HSE** in Japan.

10/7/11 (Item 4 from file: 73)
DIALOG(R)File 73:EMBASE

06598918 EMBASE No: 1996263626
Analysis of **herpes** simplex virus type 1 glycoprotein D nucleotide sequence in human **herpes** simplex **encephalitis**
Rozenberg F.; Lebon P.
Lab. de recherche infections virales, Hopital Saint-Vincent de Paul, Universite Rene Descartes 82, avenue Denfert-Rochereau,75674 Paris, cedex 14 France
Journal of NeuroVirology (J. NEUROVIROL.) (United Kingdom) 1996, 2/4 (289-295)
CODEN: JNVIF ISSN: 1355-0284
DOCUMENT TYPE: Journal; Article
LANGUAGE: ENGLISH SUMMARY LANGUAGE: ENGLISH

Viral factors responsible for **HSV** neurovirulence in humans are still unknown. The aim of this work was to investigate the hypothesis that viral variants might contribute to the specific neurovirulence of some **HSV** strains. **HSV**-1 DNA was recovered from cerebrospinal fluid (CSF) in ten patients with **HSV encephalitis** (**HSE**) and the regions of **HSV**-1 gD gene corresponding to known antigenic sites were analyzed by direct sequencing of PCR products. Twenty-two mutations were found among a total of 6580 bp analyzed over a portion of 1000 bp of gD gene, of which 20 were silent whereas two conferred amino acid substitution. One missense mutation (E117D) was found in two CSF samples as well as in two control laboratory strains. The other one (A269T) was found in a single CSF sample, and lies within a region corresponding to a functionally essential antigenic site. These are the first mutations of the gene encoding gD of **HSV** identified in vivo in human **encephalitis** samples. Overall, the results against the role of gD in neurovirulence in humans.

10/7/12 (Item 5 from file: 73)

06553422 EMBASE No: 1996214057
Clinical implications of nucleic acid amplification methods for the diagnosis of viral infections of the nervous system
Weber T.; Frye S.; Bodemer M.; Otto M.; Luke W.
Neurologische Klinik, Marienkrankenhaus Hamburg, Alfredst. 9,D-22087 Hamburg Germany
Journal of NeuroVirology (J. NEUROVIROL.) (United Kingdom) 1996, 2/3 (175-190)
CODEN: JNVIF ISSN: 1355-0284
DOCUMENT TYPE: Journal; Article
LANGUAGE: ENGLISH SUMMARY LANGUAGE: ENGLISH

Amplification of viral nucleic acids from the cerebrospinal fluid (CSF) has considerably improved the diagnosis of several acute, subacute and chronic viral infections of the nervous system. In **herpes** simplex virus (**HSV**) **encephalitis** (**HSE**) the polymerase chain reaction (PCR) has became the method of choice for the rapid, non invasive diagnosis. Other **herpes** virus associated diseases which can now be reliably diagnosed are **encephalitis**, ventriculoencephalitis, polymyeloradiculitis, myelitis and an inflammatory polyradiculoneuropathy caused by cytomegalovirus (CMV), **HSV**, varicellazoster virus (VZV) or Epstein-Barr virus (EBV), EBV associated primary B-cell-lymphoma of the brain, acute aseptic meningitis in young adults allied with VZV, and meningoencephalitis with recurrent seizures due to human **herpes** virus type 6 (HHV-6). In AIDS patients, PCR has helped to differentiate lesions either due to the human immunodeficiency virus (HIV) itself or to opportunistic infections such as progressive multifocal leukoencephalopathy (PML) caused by JC virus (JCV) or CMV related complications. HIV can be detected early in the course of infection in the CSF and the amount of proviral DNA in CSF cells seems to be correlated with the severity and/or

progression of neurological signs and symptoms. Acute epidemic aseptic meningitis caused by enterovirus infections can now be reliably diagnosed and typed by reverse transcriptase PCR (RT-PCR). Meningitis cases caused by vaccination with the Jeryl Lynn and Urabe vaccine strain of mumps virus have been identified using RT-PCR and sequencing of the amplified products (amplicon).

10/7/13 (Item 6 from file: 73)
DIALOG(R)File 73:EMBASE

06545755 EMBASE No: 1996205952
Detection of **herpes** simplex virus (types 1 and 2) and human herpesvirus 6 DNA in human brain tissue by polymerase chain reaction
Gordon L.; McQuaid S.; Cosby S.L.
The Queen's University Belfast, Division Molecular Biology, School Biology/Biochemistry, 97 Lisburn Road,Belfast BT9 7BL United Kingdom
Clinical and Diagnostic Virology (CLIN. DIAGN. VIROL.) (Netherlands) 1996, 6/1 (33-40)
CODEN: CDVIE ISSN: 0928-0197
DOCUMENT TYPE: Journal; Article
LANGUAGE: ENGLISH SUMMARY LANGUAGE: ENGLISH

Background: Previous studies, using a variety of techniques to determine whether **herpes** simplex virus type 1 (**HSV**-1) and/or type 2 (**HSV**-2) are present in normal brains or have a higher incidence in either multiple sclerosis (MS) or psychiatric disorders have yielded conflicting results. Similarly, studies to examine human brain tissue for human **herpes** virus 6 (HHV-6) have also proved inconsistent. These discrepancies may be partially due to differences in sensitivity of the methods used. Objectives: To determine whether: (i) Herpesvirus latency is a normal occurrence in the human. central nervous system (CNS), (ii) the incidence of latency is higher in either demyelinating diseases or schizophrenia: (iii) significant virus reactivation occurs in demyelinating diseases. Study Design: Frozen brain tissue from 7 cases of MS/demyelinating disease, 6 cases of schizophrenia and 27 non-neurological and a neurological controls were examined by polymerase chain reaction (PCR) for the presence of **HSV**-1 DNA. Tissue from the above catagories (except schizophrenia) were also examined for **HSV**-2 and HHV-6 DNA. In situ hybridization (ISH) and immunocytochemistry (ICC) were carried out in formalin-fixed paraffin sections from selected **HSV** PCR positive cases, including a case of **HSV encephalitis** (**HSE**).
Results: Cases from all groups were found to be positive for **HSV**-1 by PCR. Only one case (MS) was found positive for **HSV**-2, whereas HHV-6 DNA was present in 18 of 23 brains (MS and controls). Only the **HSE** case gave positive results with ISH and ICC techniques. Conclusions: These results suggest that herpesvirus latency in the human CNS is a common occurrence but there is no obvious correlation with increased incidence in either demyelinating disease or schizophrenia. Furthermore, failure to detect virus by ISH or ICC (except in a case of **HSE**) indicates lack of any significant virus reactivation in demyelinating diseases.

10/7/14 (Item 1 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

09251177 97090098
Magnetic resonance imaging of **herpes** simplex **encephalitis**.
Shian WJ; Chi CS
Department of Pediatrics, Tao-Yuan Veterans Hospital, Taiwan, R.O.C.
Chung Hua Min Kuo Hsiao Erh Ko I Hsueh Hui Tsa Chih (TAIWAN) Jan-Feb **1996**, 37 (1) p22-6, ISSN 0001-6578 Journal Code: 1M6
Languages: ENGLISH
Document type: JOURNAL ARTICLE

Eight brain magnetic resonance imagings (MRIs) and one spinal MRI of 7 small infants and children with **herpes** simplex **encephalitis** (**HSE**) were retrospectively studied. Hypointense and hyperintense areas of gray and white matters on T1- and T2- weighted images, respectively, were commonly present, with temporal lobes being the most common lesion sites. Hemorrhagic lesions were found in 4 patients (57%). Early involvement of the white matter, as early as day 4, was a common MRI finding in these patients. One patient had relapsed encephalomyelitis, whose spinal MRI showed diffuse hyperintense T2 signals from the lumbar spinal cord to the conus medullaris. All patients but one survived with major neurological sequelae. Our results indicate that MRI is a sensitive diagnostic modality in cases of **HSE**, and early involvement of white matter is not an uncommon MRI finding of **HSE**. Spinal MRI may be helpful in the diagnosis of relapsed **herpes** encephalomyelitis.

e au=lakeman fred

Ref	Items	Index-term
E1	16	AU=LAKEMAN F.D.
E2	15	AU=LAKEMAN FD
E3	3	*AU=LAKEMAN FRED
E4	7	AU=LAKEMAN FRED D
E5	2	AU=LAKEMAN G
E6	6	AU=LAKEMAN J
E7	4	AU=LAKEMAN J.
E8	2	AU=LAKEMAN J.M.
E9	1	AU=LAKEMAN JM
E10	1	AU=LAKEMAN L.
E11	2	AU=LAKEMAN M
E12	1	AU=LAKEMAN M H

Enter P or PAGE for more

? s e1-e3

	16	AU=LAKEMAN F.D.
	15	AU=LAKEMAN FD
	3	AU=LAKEMAN FRED
S15	34	E1-E3

? rd s15

...completed examining records

S16	20	RD S15 (unique items)

? s s16 and herpes

	20	S16
	115780	HERPES
S17	19	S16 AND HERPES

? t s17/7/all

17/7/1 (Item 1 from file: 5)
DIALOG(R)File 5:BIOSIS PREVIEWS(R)

11725516 BIOSIS NO.: 199800507247
Pharmacokinetics of oral valacyclovir and acyclovir in late pregnancy.
AUTHOR: Kimberlin Debora F(a); Weller Stephen; Whitley Richard J; Andrews William W; Hauth John C; **Lakeman Fred**; Miller Gerri
AUTHOR ADDRESS: (a)Dep. Obstetrics Gynecol., 618 S. 20th St., Old Hillman Build., Room 452, Birmingham, AL 35233-73**USA
JOURNAL: American Journal of Obstetrics and Gynecology 179 (4):p846-851 Oct., 1998
ISSN: 0002-9378
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: OBJECTIVE: The objective was to obtain preliminary pharmacokinetic data for acyclovir from gravid women receiving **herpes** simplex virus suppressive therapy with the acyclovir prodrug valacyclovir. STUDY DESIGN: In a prospective. double-blind trial, 20 women with a history of recurrent genital **herpes** simplex virus infection and positive **herpes** simplex virus 2 serologic results were randomly assigned at 36 weeks' gestation lo receive oral

valacyclovir (500 mg twice daily) or acyclovir (400 mg 3 times daily). Acyclovir pharmacokinetic profiles were obtained after the initial dose (36 weeks) and at steady state (38 weeks). Amniotic fluid samples were obtained during labor and simultaneous umbilical cord and maternal plasma samples were collected at delivery. Laboratory studies were performed to screen for laboratory evidence of toxicity in mothers and infants. RESULTS: Peak acyclovir plasma concentrations (mean +- standard deviation) were higher in valacyclovir recipients than in acyclovir recipients after the initial dose (3.14 +- 0.7 mug/mL vs 0.74 +- 0.6 mug/mL, P < .0001) and at steady state (3.03 +- 1.0 mug/mL vs 0.94 +- 0.7 mug/mL, P < .001). The daily area under the curve values were higher in valacyclovir recipients than acyclovir recipients after the initial dose (17.8 +- 3.6 h cntdot mug/mL vs 7.71 +- 2.5 h cntdot mug/mL, P < .001) and at steady state (19.65 +- 6.4 h cntdot mug/mL versus 11.0 +- 4.5 h cntdot mug/mL, P = .009). There was no significant difference in drug elimination half-life or in time to peak concentration between valacyclovir and acyclovir recipients at either sampling interval. Acyclovir was concentrated in the amniotic fluid; however, there was no evidence of preferential fetal drug accumulation (mean maternal/umbilical vein plasma ratios at delivery were 1.7 for valacyclovir and 1.3 for acyclovir). Valacyclovir was well tolerated, and no significant laboratory or clinical evidence of toxicity was detected. CONCLUSION: In this phase I trial maternal valacyclovir therapy resulted in higher plasma acyclovir levels, with significantly higher peak concentrations and daily area under the curve values, than did acyclovir therapy. Additional trials are needed to further evaluate the safety and efficacy of suppressive valacyclovir therapy during late pregnancy.

17/7/2 (Item 2 from file: 5)
DIALOG(R)File 5:BIOSIS PREVIEWS(R)

09718216 BIOSIS NO.: 199598173134
Herpes simplex virus infections of the central nervous system: Therapeutic and diagnostic considerations.
AUTHOR: Whitley Richard J(a); **Lakeman Fred**
AUTHOR ADDRESS: (a)Univ. Alabama Sch. Medicine, Dep. Pediatr., 616 Children's Hosp., 1600 Seventh Ave. South, Birmi**USA
JOURNAL: Clinical Infectious Diseases 20 (2):p414-420 1995
ISSN: 1058-4838
DOCUMENT TYPE: Literature Review
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: **Herpes** simplex virus infections of the central nervous system remain a significant cause of morbidity and mortality, in spite of safe and efficacious antiviral therapy. Advances in the treatment of neonatal **herpes** and **herpes** simplex encephalitis with acyclovir have improved outcome. The application of polymerase chain reaction has allowed for the prompt and specific diagnosis of **herpes** simplex virus infections of the brain. This review summarizes our current knowledge on the pathogenesis, diagnosis, and treatment of **herpes** simplex virus infections of the brain. Opportunities for the future will be defined.

17/7/3 (Item 3 from file: 5)
DIALOG(R)File 5:BIOSIS PREVIEWS(R)

08682254 BIOSIS NO.: 199345100329
Herpes simplex encephalitis: Overview and diagnostic considerations.
BOOK TITLE: Antiviral Chemotherapy
AUTHOR: **Lakeman Fred**(a); Whitley Richard J
BOOK AUTHOR/EDITOR: Mills J; Corey L: Eds

AUTHOR ADDRESS: (a)Dep. Pediatr., Univ. Alabama, Birmingham, AL**USA
JOURNAL: Antiviral Chemotherapy 3p21-31 1993
BOOK PUBLISHER: Prentice-Hall, Inc., 113 Sylvan Avenue, Route 9W, Englewood Cliffs, New Jersey 07623, USA
Prentice-Hall, London, England, UK
CONFERENCE/MEETING: Third Triennial Conference on Antiviral Chemotherapy San Francisco, California, USA November 1991
ISBN: 0-13-050717-2
DOCUMENT TYPE: Article
RECORD TYPE: Citation
LANGUAGE: English

17/7/4 (Item 1 from file: 73)
DIALOG(R)File 73:EMBASE

07507799 EMBASE No: 1998398390
Comparison of antiviral compounds against human herpesvirus 6 and 7
Yoshida M.; Yamada M.; Tsukazaki T.; Chatterjee S.; **Lakeman F.D.**; Nii S.; Whitley R.J.
M. Yoshida, Department of Virology, Okayama University Med. School, 2-5-1 Shikatacho, Okayama 700-8558 Japan
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Antiviral Research (ANTIVIRAL RES.) (Netherlands) 1998, 40/1-2 (73-84)
CODEN: ARSRD ISSN: 0166-3542
PUBLISHER ITEM IDENTIFIER: S0166354298000497
DOCUMENT TYPE: Journal; Article
LANGUAGE: ENGLISH SUMMARY LANGUAGE: ENGLISH
NUMBER OF REFERENCES: 59

Four classes of antiviral compounds were evaluated for inhibitory activity against two variants of human herpesvirus 6 (HHV-6A and -6B) and human herpesvirus 7 (HHV-7). These included: (1) a pyrophosphate analog, phosphonoformic acid (PFA); (2) beta-guanine analogs, 9-(2-hydroxyethoxymethyl)guanine (acyclovir or ACV), 9-[(1,3-dihydroxy-2-propoxy)methyl]guanine (ganciclovir or GCV) and 9-(4-hydroxy-3-hydroxy-3-hydroxymethylbutylyl)guanine (penciclovir or PCV); (3) acyclic nucleoside phosphonates, (S)-1-[(3-hydroxy-2-phosphonylmethoxy)propyl]cytosine [cidofovir or (S)-HPMPC] and its cyclic derivative (S)-cyclic-HPMPC (cHPMPC), 9-[[2-hydroxy-1-phosphonomethoxy)ethoxy]methyl]guanine (HPMEMG) and 9-[(2-phosphonylmethoxy)ethyl]-2,6-diaminopurine (PMEDAP), and the seven other related compounds; and (4) a series of benzimidazole ribonucleosides, including 2-bromo-5,6-dichloro-1-(beta-d-ribofuranosyl)benzimidazole (BDCRB). End-point inhibitory concentration (EPC) and 50% effective inhibitory concentration (EC$D5inf 0) values were determined by a dot-blot antigen detection method in cord blood mononuclear cells infected with HHV-6A, HHV-6B or HHV-7 at a multiplicity of infection of 0.004 CCID$D5inf 0/cell. (S)-HPMPC and cHPMPC had an EC$D5inf 0 value of approximately 0.3 mug/ml for HHV-6A, 1.2 mug/ml for HHV-6B and 3.0 mug/ml for HHV-7. These compounds were the most active of those tested against each virus. The EC$D5inf 0 value of GCV for HHV-6A was 0.65 mug/ml, 1.33 mug/ml for HHV-6B, and >7 mug/ml for HHV-7. The EC$D5inf 0 values of ACV and PCV were approximately 6-8 mug/ml for HHV-6A, 16-24 mug/ml for HHV-6B and 121-128 mug/ml for HHV-7. These drugs were the least active. The sensitivity of HHV-7 to the guanine analogs was different from HHV-6, suggesting a difference in selectivity of specific viral enzymes. Copyright (C) 1998 Elsevier Science B.V.

17/7/5 (Item 2 from file: 73)
DIALOG(R)File 73:EMBASE

07356829 EMBASE No: 1998236175

Application of competitive PCR to cerebrospinal fluid samples from patients with **herpes** simplex encephalitis

Domingues R.B.; **Lakeman F.D.**; Mayo M.S.; Whitley R.J.
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Journal of Clinical Microbiology (J. CLIN. MICROBIOL.) (United States) 1998, 36/8 (2229-2234)
CODEN: JCMID ISSN: 0095-1137
DOCUMENT TYPE: Journal; Article
LANGUAGE: ENGLISH SUMMARY LANGUAGE: ENGLISH
NUMBER OF REFERENCES: 36

The purpose of the present study was to determine if the quantity of **herpes** simplex virus (HSV) DNA in the cerebrospinal fluid (CSF) of patients with **herpes** encephalitis would be useful in establishing the prognosis of the disease and to determine the effect of antiviral therapy on the clearance of viral DNA from the CSF. Quantitation of HSV DNA was done by constructing an internal standard (IS) from the glycoprotein B amplicon which had a 25-bp deletion between primer annealing sites. Each CSF specimen was coamplified with the IS and the ratio of the amount of HSV/amount of IS was compared to the ratios on a standard curve constructed with the same IS plus known amounts of HSV DNA. CSF specimens were available from 16 patients who were treated with intravenous acyclovir, and the amount of HSV DNA ranged from <25 to 18,000 copies per mul in CSF obtained before or within 4 days of the initiation of acyclovir therapy. Patients with >100 copies of HSV DNA per mul were older, were found by computed tomography to have lesions, and had poorer outcomes than patients with <100 copies. Follow-up CSF specimens were available from seven patients. In six of these seven patients, the HSV DNA levels decreased during therapy. One patient had a twofold increase in HSV DNA levels after 1 week of therapy and died on day 8. The application of this assay may be helpful in establishing the prognosis and in the monitoring of patients with **herpes** simplex encephalitis.

17/7/6 (Item 3 from file: 73)
DIALOG(R)File 73:EMBASE

07263079 EMBASE No: 1998160083

Diagnosis of **herpes** simplex encephalitis by magnetic resonance imaging and polymerase chain reaction assay of cerebrospinal fluid

Domingues R.B.; Fink M.C.D.; Tsanaclis A.M.C.; de Castro C.C.; Cerri G.G.; Mayo M.S.; **Lakeman F.D.**
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Journal of the Neurological Sciences (J. NEUROL. SCI.) (Netherlands) 1998, 157/2 (148-153)
CODEN: JNSCA ISSN: 0022-510X
PUBLISHER ITEM IDENTIFIER: S0022510X98000690
DOCUMENT TYPE: Journal; Article
LANGUAGE: ENGLISH SUMMARY LANGUAGE: ENGLISH
NUMBER OF REFERENCES: 15

The early diagnosis of **herpes** simplex encephalitis (HSE) is essential because early introduction of antiviral therapy can significantly reduce the mortality of this disease. **Herpes** simplex virus (HSV) DNA detection in cerebrospinal fluid (CSF) samples is a rapid, noninvasive, specific, and highly sensitive method for HSE diagnosis. Neurodiagnostic methods have also been studied for noninvasive diagnosis of HSE. Magnetic resonance imaging (MRI) seems to be the most sensitive of them but it has not been compared to PCR in terms of efficacy for HSE diagnosis. In this study, 17 patients with focal encephalitis were prospectively evaluated by PCP, analysis of CSF samples and MRI examination. MRI lesions involving the

inferomedial region of one or both temporal lobes were observed in all PCR-positive patients but one. No PCR-negative patient presented with the same pattern of MRI lesions. MRI was also important for the establishment of an alternative diagnosis in three of eight PCR-negative patients. Both methods should be routinely applied in the evaluation of presumed HSE cases.

17/7/7 (Item 4 from file: 73)
DIALOG(R)File 73:EMBASE

06973771 EMBASE No: 1997258371
Advantage of polymerase chain reaction in the diagnosis of **herpes** simplex encephalitis: Presentation of 5 atypical cases
Domingues R.B.; **Lakeman F.D.**; Pannuti C.S.; Fink M.C.D.; Tsanaclis A.M.C.
Dr. R.B. Domingues, R. Frei Caneca 617, Sao Paulo, SP 01307-001 Brazil
Scandinavian Journal of Infectious Diseases (SCAND. J. INFECT. DIS.) (Norway) 1997, 29/3 (229-231)
CODEN: SJIDB ISSN: 0036-5548
DOCUMENT TYPE: Journal; Article
LANGUAGE: ENGLISH SUMMARY LANGUAGE: ENGLISH
NUMBER OF REFERENCES: 22

Four cases of **herpes** encephalitis (HSVE) are described. The diagnosis was established by polymerase chain reaction (PCR) assay of cerebrospinal fluid (CSF). These reports illustrate different situations in the clinical management of this disease. PCR was considered useful in confirming the HSVE diagnosis in 3 atypical cases, and in the differentiation between virologic failure and postinfectious encephalitis in a patient with recurrence of symptoms. A case with typical HSVE clinical findings is also reported where PCR was negative and a temporal lobe lymphoma was diagnosed at autopsy. This last case is representative of the utility of PCR in the management of other diseases mimicking HSVE.

17/7/8 (Item 5 from file: 73)
DIALOG(R)File 73:EMBASE

06924643 EMBASE No: 1997209114
Evaluation of the range of clinical presentations of **herpes** simplex encephalitis by using polymerase chain reaction assay of cerebrospinal fluid samples
Domingues R.B.; Tsanaclis A.M.C.; Pannuti C.S.; Mayo M.S.; **Lakeman F.D.**
Dr. R.B. Domingues, R. Frei Caneca 617, 94 Sao Paulo, SP 01307-001 Brazil
Clinical Infectious Diseases (CLIN. INFECT. DIS.) (United States) 1997, 25/1 (86-91)
CODEN: CIDIE ISSN: 1058-4838
DOCUMENT TYPE: Journal; Article
LANGUAGE: ENGLISH SUMMARY LANGUAGE: ENGLISH
NUMBER OF REFERENCES: 33

Detection of DNA from **herpes** simplex virus in cerebrospinal fluid (CSF) samples by polymerase chain reaction (PCR) analysis has been shown to be more sensitive and specific for the diagnosis of **herpes** simplex encephalitis than isolation of **herpes** simplex virus from biopsy specimens of brain tissue. Because of the invasiveness of brain biopsy, it has been suggested that PCR analysis of CSF may reveal a wider spectrum of the disease than has been previously recognized by brain biopsy studies. In this study, PCR assay of CSF samples obtained from 29, 12, and 8 patients with focal, mild, and diffuse encephalitis, respectively, was performed. PCR assay was positive for 15 (51.7%) of 29 patients with focal

encephalitis and three (25%) of 12 patients with mild encephalitis. The correlation between temporal abnormalities shown by electroencephalography, computed tomography of the brain, or cranial magnetic resonance imaging and a positive PCR assay was high. PCR analysis has revealed that atypical and less severe forms of encephalitis are caused by **herpes** simplex virus.

17/7/9 (Item 6 from file: 73)
DIALOG(R)File 73:EMBASE

06693950 EMBASE No: 1996358887
Application of the polymerase chain reaction to the diagnosis and management of neonatal **herpes** simplex virus disease
Kimberlin D.W.; **Lakeman F.D.**; Arvin A.M.; Prober C.G.; Corey L.; Powell D.A.; Burchett S.K.; Jacobs R.F.; Starr S.E.; Whitley R.J.; Soong S.-J.; Stagno S.; Pass R.; Robinson J.; Vaudry W.; Bradley J.; Spector S.; Kovacs A.; Bryson Y.; et al.
University of Alabama, 1600 7th Ave. S.,Birmingham, AL 35233 United States
Journal of Infectious Diseases (J. INFECT. DIS.) (United States) 1996, 174/6 (1162-1167)
CODEN: JIDIA ISSN: 0022-1899
DOCUMENT TYPE: Journal; Article
LANGUAGE: ENGLISH SUMMARY LANGUAGE: ENGLISH

Cerebrospinal fluid (CSF) specimens from 77 neonates with **herpes** simplex virus (HSV) disease were evaluated retrospectively by polymerase chain reaction (PCR). Samples were collected from 202 infants enrolled in a National Institute of Allergy and Infectious Diseases Collaborative Antiviral Study Group trial that compared vidarabine with acyclovir for the treatment of neonatal HSV infection. HSV DNA was detected in the CSF of 26 (76%) of 34 infants with CNS disease, in 13 (93%) of 14 infants with disseminated infection, and in 7 (24%) of 29 with skin, eye, or mouth (SEM) involvement. One of the 7 PCR-positive SEM patients subsequently developed severe neurologic impairment. Eighteen (95%) of 19 infants with positive CSF PCR results after the completion of 10 days of antiviral therapy experienced significant morbidity or mortality. Application of PCR to neonatal HSV disease may provide additional information on which clinical decisions may be based, although its diagnostic utility outside the research setting is unproven.

17/7/10 (Item 7 from file: 73)
DIALOG(R)File 73:EMBASE

06081831 EMBASE No: 1995112318
Diagnosis of **herpes** simplex encephalitis: Application of polymerase chain reaction to cerebrospinal fluid from brain-biopsied patients and correlation with disease
Lakeman F.D.; Whitley R.J.; Alford C.; Cobbs C.G.; Morawetz R.; Soong S.; Hirsch M.S.; Dolan R.; Betts R.; Reichman R.; Corey L.; Levin M.; Handley D.; Connor J.; Spector S.; Oxman M.; Richman D.; Hayden F.; Greenlee J.; et al.
Dept. of Pediatrics, University of Alabama, S. UAB Station, 845 19th St.,Birmingham, AL 35294 United States
Journal of Infectious Diseases (J. INFECT. DIS.) (United States) 1995, 171/4 (857-863)
CODEN: JIDIA ISSN: 0022-1899
DOCUMENT TYPE: Journal; Article
LANGUAGE: ENGLISH SUMMARY LANGUAGE: ENGLISH

Isolation of **herpes** simplex virus (HSV) from brain tissue after biopsy has been considered the reference standard for the diagnosis of **herpes** simplex encephalitis (HSE). During the evaluation of antiviral

treatment of HSE, cerebrospinal fluid (CSF) was obtained from patients with clinical disease indicative of HSE who underwent diagnostic brain biopsy. HSV DNA was detected by polymerase chain reaction (PCR) in CSF of 53 (98%) of 54 patients with biopsy-proven HSE and was detected in all 18 CSF specimens obtained before brain biopsy from patients with proven HSE. Four of 19 CSF specimens were positive after 2 weeks of antiviral therapy. Positive results were found in 3 (6%) of 47 patients whose brain tissue was culture-negative. Detection of HSV DNA in the CSF correlated significantly with age and focal radiographic findings. Thus, PCR detection of HSV DNA should be the standard for diagnosis of HSE.

17/7/11 (Item 8 from file: 73)
DIALOG(R)File 73:EMBASE

04172454 EMBASE No: 1990054996
Rapid detection of **herpes**-simplex-virus DNA in cerebrospinal fluid of patients with **herpes** simplex encephalitis
Rowley A.H.; Whitley R.J.; **Lakeman F.D.**; Wolinsky S.M.
Department of Pediatrics, Northwestern University, Chicago, IL United States
Lancet (LANCET) (United Kingdom) 1990, 335/8687 (440-441)
CODEN: LANCA ISSN: 0140-6736
DOCUMENT TYPE: Journal; Article
LANGUAGE: ENGLISH SUMMARY LANGUAGE: ENGLISH

Herpes-simplex-virus (HSV) DNA in cerebrospinal fluid was amplified by use of the polymerase chain reaction and identified by hybridisation to a specific oligonucleotide probe. Specimens of cerebrospinal fluid (CSF) from 4 of 4 patients with **herpes** simplex encephalitis were positive for HSV DNA, whereas CSF specimens from 6 patients with other central-nervous-system infections were negative. this technique may expedite diagnosis of **herpes** simplex encephalitis.

17/7/12 (Item 9 from file: 73)
DIALOG(R)File 73:EMBASE

03756745 EMBASE No: 1988206181
An isoelectric focusing study in **herpes** simplex virus encephalitis
Grimaldi L.M.E.; Roos R.P.; Manservigi R.; Spear P.G.; **Lakeman F.D.**; Whitley R.J.
Department of Neurology, University of Chicago, Chicago, IL 60637 United States
Annals of Neurology (ANN. NEUROL.) (United States) 1988, 24/2 (227-232)
CODEN: ANNED ISSN: 0364-5134
DOCUMENT TYPE: Journal
LANGUAGE: ENGLISH SUMMARY LANGUAGE: ENGLISH

To establish an early reliable diagnostic test for **herpes** simplex virus (HSV) type 1 encephalitis (HSVE), we used isoelectric focusing (IEF) and an IEF-overlay technique with radiolabeled HSV glycoprotein B (gB) to study 7 and 12 cerebrospinal fluid (CSF) samples from 12 patients with presumed or biopsy-proved HSVE. Blood-brain barrier damage and increased intra-blood-brain IgG synthesis were detected in 5 of the 7 patients with HSVE. CSF oligoclonal bands were found in 6 of 11 patients. Using an IEF-overlay technique, we detected ant-gB antibody in all serum (7 of 7) and in 10 of 12 CSF samples. Anti-gB antibody was found in 4 of 6 CSF specimens obtained within the first week of disease (day 3 to 5) and in all samples collected later in the disease. The Ph range of anti-gB antibody activity was broad (4.5 to 9.5), indicating a heterogeneous immune response to HSV. A hematogenous origin of the CSF antibody was suggested because anti-gB antibody appeared in serum before matched CSF and because both

serum and matched CSF had a similar antibody IEF pattern. Local production of anti-gB antibody was suggested in some cases because of a greater prominence of anti-gB antibody in CSF than in matched sera because CSF oligoclonal bands had anti-gB antibody activity. In contrast, only one of 6 CSF samples from patients with multiple sclerosis had gB antibody activity; in this case, anti-gB antibody activity did not correspond in isoelectric point location to oligoclonal bands. The IEF-HSV-gB overlay technique may be a useful diagnostic test for HSVE and a valuable research tool for studying qualitative aspects of the HSV humoral immune response.

17/7/13 (Item 10 from file: 73)
DIALOG(R)File 73:EMBASE

03739570 EMBASE No: 1988189006
Changing patterns of **herpes** simplex virus infection in neonates
Whitley R.J.; Corey L.; Arvin A.; **Lakeman F.D.**; Sumaya C.V.; Wright P.F.; Dunkle L.M.; Steele R.W.; Soong S.-J.; Nahmias A.J.; Alford C.A.; Powell D.A.; Joaquin V.S.; Benton J.; Hutto C.; Caddell G.; Snead O.; Brady M.; Conner J.; et al.
University of Alabama, Birmingham, AL United States
Journal of Infectious Diseases (J. INFECT. DIS.) (United States) 1988 , 158/1 (109-116)
CODEN: JIDIA ISSN: 0022-1899
DOCUMENT TYPE: Journal
LANGUAGE: ENGLISH SUMMARY LANGUAGE: ENGLISH

We compared the clinical presentation of 95 newborns with **herpes** simplex virus (HSV) infection from 1973 through 1981 (first period) with data from 196 newborns evaluated from 1982 through 1987 (second period). There was a significant change in the presentation of infection in these infants. From the first to the second period, the frequency of disseminated disease decreased from 50.5% to 22.9%, whereas the frequency of skin, eye, and mouth (SEM) diseases increased from 17.9% to 43.4% ($P < .001$). The frequency of infants with central nervous system (CNS) disease remained relatively unchanged - 31.6% versus 33.7%. We also compared the demographic and clinical characteristics of the infants and their mothers. For neonates with CNS or disseminated infection, disease duration and frequency of prematurity were significantly decreased in the second period, as was the frequency of skin vesicles for newborns with SEM or disseminated infection. These changes are most likely the consequence of recognizing and treating SEM infection before its progression to more-severe disease.

17/7/14 (Item 11 from file: 73)
DIALOG(R)File 73:EMBASE

03540000 EMBASE No: 1987056936
Detection of antibodies to **herpes** simplex virus in the cerebrospinal fluid of patients with **herpes** simplex encephalitis
Kahlon J.; Chatterjee S.; **Lakeman F.D.**; et al.
Department of Pediatrics, University of Alabama at Birmingham, Birmingham, AL United States
Journal of Infectious Diseases (J. INFECT. DIS.) (United States) 1987 , 155/1 (38-44)
CODEN: JIDIA
DOCUMENT TYPE: Journal
LANGUAGE: ENGLISH

Cerebrospinal fluid (CSF) and serum specimens from patients with presumed **herpes** simplex encephalitis (HSE) were characterized for antibodies to **herpes** simplex virus (HSV) by immunoblot and other immunoassays. Specimens from patients proven to have HSE (biopsy-proven) were compared with those from patients with other diseases diagnosed by brain biopsy

(biopsy-negative for HSV). Immunoblot of CSF demonstrated that antibodies to HSV-specific polypeptides, particularly to glycoprotein B, were present in a matched serum specimen. When purified glycoprotein B was used to detect CSF antibodies, 34 of 35 specimens from biopsy-proven patients were reactive (97% sensitivity) compared with only six of 22 specimens obtained from biopsy-negative patients (73% specificity). If leakage of antibodies to a marker virus (adenovirus) was determined and controlled, the specificity increased to 100%. These diagnostic assays provide useful tools for the retrospective assessment of CSF specimens obtained from patients with presumed HSE.

17/7/15 (Item 12 from file: 73)
DIALOG(R)File 73:EMBASE

03395414 EMBASE No: 1987147991
Detection of antigen to **herpes** simplex virus in cerebrospinal fluid from patients with **herpes** simplex encephalitis
Lakeman F.D.; Koga J.; Whitley R.J.
Department of Pediatrics, University of Alabama at Birmingham School of Medicine, Birmingham, AL 35294 United States
Journal of Infectious Diseases (J. INFECT. DIS.) (United States) 1987, 155/6 (1172-1178)
CODEN: JIDIA
DOCUMENT TYPE: Journal
LANGUAGE: ENGLISH

Cerebrospinal fluid (CSF) specimens were obtained from patients with presumed **herpes** simplex encephalitis who underwent brain biopsy for diagnostic confirmation. Coded CSF specimens were fixed on nitrocellulose filter paper and probed with a pool of monoclonal antibodies directed against four **herpes** simplex virus glycoproteins (gB, gC, gD, and gE). **Herpes** simplex virus antigen was detected in 35 of 40 specimens obtained from 26 biopsy-positive patients. In contrast, only three of 25 specimens from 17 biopsy-negative patients gave positive results by this assay. An additional 30 CSF specimens from patients with proven bacterial and fungal infections were all negative by this assay. For all specimens tested, the sensitivity and specificity of the assay were both 88%. However, when results were evaluated by patient, the sensitivity was 92% (24 of 26) with a specificity of 82% (14 of 17). Among specimens colleced one week or later after disease onset, the sensitivity was 100%, with a specificity of 93%.

17/7/16 (Item 13 from file: 73)
DIALOG(R)File 73:EMBASE

03261244 EMBASE No: 1986058821
Psychosis and **herpes** simplex encephalitis
Schlitt M.; **Lakeman F.D.**; Whitley R.J.
Division of Neurosurgery, University of Alabama School of Medicine, University Station, Birmingham, AL 35294 United States
Southern Medical Journal (SOUTH. MED. J.) (United States) 1985, 78/11 (1347-1350)
CODEN: SMJOA
DOCUMENT TYPE: Journal
LANGUAGE: ENGLISH

We have reported an unusual presentation of **herpes** simplex encephalitis in a patient with a 31/2-year history of a schizo-affective disorder. In the month immediately before diagnosis, the patient lost contact with reality and became violent. After successful treatment with antipsychotic medication, he had agitation and disorientation, as well as fever and cerebrospinal fluid pleocytosis. There were no focal neurologic

findings. When a low-density lesion in the right temporal lobe was defined by computerized axial tomography, brain biopsy and culture isolated **herpes** simplex virus type 1. After therapy with vidarabine, the patient regained independence in simple daily activities. This case stresses the possibility of **herpes** simplex encephalitis in patients with an acute mental change.

17/7/17 (Item 14 from file: 73)
DIALOG(R)File 73:EMBASE

03193267 EMBASE No: 1986125844
Human antibody response to **herpes** simplex virus-specific polypeptides after primary and recurrent infection
Kahlon J.; **Lakeman F.D.**; Ackermann M.; Whitley R.J.
Department of Pediatrics, University of Alabama, Birmingham, AL 35294 United States
Journal of Clinical Microbiology (J. CLIN. MICROBIOL.) (United States) 1986, 23/4 (725-730)
CODEN: JCMID
DOCUMENT TYPE: Journal
LANGUAGE: ENGLISH

Human antibody responses to specific polypeptides of **herpes** simplex virus type 1 and 2 (HSV-1 and HSV-2, respectively) were assessed in serial serum specimens from 18 infected patients by immunoblot technology. Nine patients had HSV-1 infections (six genital and three oral) and nine had HSV-2 genital infections. Antibodies to homologous and heterologous HSV antigens were studied and correlated with total microneutralization and enzyme-linked immunosorbent assay antibodies as well as correlated directly to purified glycoproteins. The data indicated a sequential appearance of antibodies to specific polypeptides, according to virus type and site of infection. After HSV-1 infection, the initial response was to glycoprotein B, but the same was not true for HSV-2 infection, where the initial response appeared to be to the type-specific glycoprotein G. A difference in sequential appearance of antibodies for the two viruses indicated greater reactivity to lower-molecular-weight polypeptides after genital infection, irrespective of type, in contrast to nongenital HSV-1 infections. The antibody responses for selected sera to purified glycoproteins B and D were verified by enzyme-linked immunosorbent assay antibody determinations.

17/7/18 (Item 1 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

08880913 97094116
Application of the polymerase chain reaction to the diagnosis and management of neonatal **herpes** simplex virus disease. National Institute of Allergy and Infectious Diseases Collaborative Antiviral Study Group.
Kimberlin DW; **Lakeman FD**; Arvin AM; Prober CG; Corey L; Powell DA; Burchett SK; Jacobs RF; Starr SE; Whitley RJ
Department of Pediatrics, University of Alabama at Birmingham, 35233, USA.
J Infect Dis (UNITED STATES) Dec 1996, 174 (6) p1162-7, ISSN 0022-1899 Journal Code: IH3
Contract/Grant No.: AI-15113, AI, NIAID; AI-62554, AI, NIAID; RR-032, RR, NCRR
Languages: ENGLISH
Document type: JOURNAL ARTICLE
Cerebrospinal fluid (CSF) specimens from 77 neonates with **herpes** simplex virus (HSV) disease were evaluated retrospectively by polymerase chain reaction (PCR). Samples were collected from 202 infants enrolled in a

National Institute of Allergy and Infectious Diseases Collaborative Antiviral Study Group trial that compared vidarabine with acyclovir for the treatment of neonatal HSV infection. HSV DNA was detected in the CSF of 26 (76%) of 34 infants with CNS disease, in 13 (93%) of 14 infants with disseminated infection, and in 7 (24%) of 29 with skin, eye, or mouth (SEM) involvement. One of the 7 PCR-positive SEM patients subsequently developed severe neurologic impairment. Eighteen (95%) of 19 infants with positive CSF PCR results after the completion of 10 days of antiviral therapy experienced significant morbidity or mortality. Application of PCR to neonatal HSV disease may provide additional information on which clinical decisions may be based, although its diagnostic utility outside the research setting is unproven.

17/7/19 (Item 2 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

05362762 88274075

Changing presentation of **herpes** simplex virus infection in neonates.

Whitley RJ; Corey L; Arvin A; **Lakeman FD**; Sumaya CV; Wright PF; Dunkle LM; Steele RW; Soong SJ; Nahmias AJ; et al

University of Alabama at Birmingham 35294.

J Infect Dis (UNITED STATES) Jul 1988, 158 (1) p109-16, ISSN 0022-1899 Journal Code: IH3

Contract/Grant No.: AI-62554, AI, NIAID; CA-13148, CA, NCI; RR-032, RR, NCRR

Languages: ENGLISH

Document type: CLINICAL TRIAL; CONTROLLED CLINICAL TRIAL; JOURNAL ARTICLE

We compared the clinical presentation of 95 newborns with **herpes** simplex virus (HSV) infection from 1973 through 1981 (first period) with data from 196 newborns evaluated from 1982 through 1987 (second period). There was a significant change in the presentation of infection in these infants. From the first to the second period, the frequency of disseminated disease decreased from 50.5% to 22.9%, whereas the frequency of skin, eye, and mouth (SEM) diseases increased from 17.9% to 43.4% (P less than .001). The frequency of infants with central nervous system (CNS) disease remained relatively unchanged--31.6% versus 33.7%. We also compared the demographic and clinical characteristics of the infants and their mothers. For neonates with CNS or disseminated infection, disease duration and frequency of prematurity were significantly decreased in the second period, as was the frequency of skin vesicles for newborns with SEM or disseminated infection. These changes are most likely the consequence of recognizing and treating SEM infection before its progression to more-severe disease.

... al., Nature 356, 63 (1992); Baron et al., J. Exp. Med. 177, 57 (1993)), meningitis, **encephalitis**, stroke, other ...interval.

t s8/3/1,6,18,24,32,33,38,39,

8/3/1 (Item 1 from file: 654)
DIALOG(R)File 654:US Pat.Full.

03055104
Utility
INHIBITORS OF LEUKOCYTE ADHESION

PATENT NO.: 6,001,809
ISSUED: December 14, 1999 (19991214)
INVENTOR(s): Thorsett, Eugene D., Moss Beach, CA (California), US (United States of America)
Yednock, Theodore A., Fairfax, CA (California), US (United States of America)
Pleiss, Michael A., Fremont, CA (California), US (United States of America)
ASSIGNEE(s): Elan Pharmaceuticals, Inc , (A U.S. Company or Corporation), South San Francisco, CA (California), US (United States of America)
APPL. NO.: 8-467,580
FILED: June 06, 1995 (19950606)

This application is a continuation-in-part of U.S. patent application Ser. No. 08-273,055 filed July 11, 1994, now abandoned, which application is incorporated herein by reference in its entirety.

FULL TEXT: 3429 lines

8/3/6 (Item 6 from file: 654)
DIALOG(R)File 654:US Pat.Full.

03012766
Utility
METHODS AND COMPOSITIONS FOR TARGETING SELECTINS

PATENT NO.: 5,962,424
ISSUED: October 05, 1999 (19991005)
INVENTOR(s): Hallahan, Dennis E., Park Ridge, IL (Illinois), US (United States of America)
Weichselbaum, Ralph R., Chicago, IL (Illinois), US (United States of America)
ASSIGNEE(s): Arch Development Corporation, (A U.S. Company or Corporation), Chicago, IL (Illinois), US (United States of America)
[Assignee Code(s): 20681]
APPL. NO.: 8-392,541
FILED: February 21, 1995 (19950221)

The U.S. Government owns rights in the present invention pursuant to grant number 58508 from the National Institutes of Health.

FULL TEXT: 3130 lines

8/3/18 (Item 18 from file: 654)
DIALOG(R)File 654:US Pat.Full.

02874753

Utility
METHOD OF IDENTIFYING MODULATORS OF BINDING BETWEEN AND VCAM-1
[Cellular adhesion molecules]

PATENT NO.: 5,837,478
ISSUED: November 17, 1998 (19981117)
INVENTOR(s): Gallatin, W. Michael, Mercer Island, WA (Washington), US (United States of America)
Van der Vieren, Monica, Seattle, WA (Washington), US (United States of America)
ASSIGNEE(s): ICOS Corporation, (A U.S. Company or Corporation), Bothell, WA (Washington), US (United States of America)
[Assignee Code(s): 36677]
APPL. NO.: 8-943,363
FILED: October 03, 1997 (19971003)

This application is a continuation-in-part of U.S. Pat. application Ser. No. 08-605,672, filed Feb. 22, 1996, which is now abandoned, which is a continuation-in-part of U.S. application Ser. No. 08-362,652, filed Dec. 21, 1994, now U.S. Pat. No. 5,766,850, which is a continuation-in-part of U.S. application Ser. No. 08-286,889, filed Aug. 5, 1994, which issued as U.S. Pat. No. 5,470,953 on Nov. 28, 1995, which in turn is a continuation-in-part of U.S. application Ser. No. 08-173,497, filed Dec. 23, 1993, which issued as U.S. Pat. No. 5,437,958 on Aug. 1, 1995.

FULL TEXT: 9188 lines

8/3/24 (Item 24 from file: 654)
DIALOG(R)File 654:US Pat.Full.

02756213

Utility
SOLUBLE ANALOGUES OF INTEGRINS

PATENT NO.: 5,726,290
ISSUED: March 10, 1998 (19980310)
INVENTOR(s): Bodary, Sarah C., San Francisco, CA (California), US (United States of America)
Gorman, Cornelia M., San Francisco, CA (California), US (United States of America)
McLean, John W., San Francisco, CA (California), US (United States of America)
Napier, Mary A., Hillsborough, CA (California), US (United States of America)
ASSIGNEE(s): Genentech, Inc , (A U.S. Company or Corporation), South San Francisco, CA (California), US (United States of America)
[Assignee Code(s): 7579]
APPL. NO.: 8-445,042
FILED: May 19, 1995 (19950519)

CROSS REFERENCES

This application is a divisional of U.S. application Ser. No. 08-380,227 filed 30 Jan. 1995, now abandoned, which application is a continuation of U.S. application Ser. No. 08-218,878 filed 28 Mar. 1994 (abandoned), which application is a continuation of U.S. application Ser. No. 07-821,337 filed 13 Jan. 1992 (abandoned), which application is a continuation of U.S. application Ser. No. 07-444,490 filed 1 Dec. 1989 (abandoned), which application is a continuation-in-part of U.S. application Ser. No. 07-290,224 filed 22 Dec. 1988 (abandoned), which applications are incorporated herein by reference and to which applications priority is

claimed under 35 USC selection 120.

FULL TEXT: 2336 lines

8/3/32 (Item 32 from file: 654)
DIALOG(R)File 654:US Pat.Full.

02616599
Utility
METHOD FOR ISOLATING A NOVEL RECEPTOR FOR .ALPHA.4 INTEGRINS
[Incubation, removal of unbound genetic engineered cells, elution of bound cells, isolation of DNA molecules]

PATENT NO.: 5,599,676
ISSUED: February 04, 1997 (19970204)
INVENTOR(s): Vonderheide, Robert H., Brookline, MA (Massachusettes), US (United States of America)
Springer, Timothy A., Chestnut Hill, MA (Massachusettes), US (United States of America)
ASSIGNEE(s): Center for Blood Research, Inc, (A U.S. Company or Corporation), Boston, MA (Massachusetts), US (United States of America)
[Assignee Code(s): 15091]
APPL. NO.: 8-323,199
FILED: October 14, 1994 (19941014)

This is a continuation of application Ser. No. 07-886,992, filed May 21, 1992, now abandoned.

This invention was made with government support under grant number CA-31798 awarded by the National Institutes of Health. The government has certain rights in the invention.

FULL TEXT: 1673 lines

8/3/33 (Item 33 from file: 654)
DIALOG(R)File 654:US Pat.Full.

02612754
Utility
ANTISENSE OLIGONUCLEOTIDES DIRECTED AGAINST HUMAN VCAM-1 RNA
[Treatment of septic shock, adult respiratory distress syndrome]

PATENT NO.: 5,596,090
ISSUED: January 21, 1997 (19970121)
INVENTOR(s): Hoke, Glenn D., Mt. Airy, MD (Maryland), US (United States of America)
Bradley, Matthews O., Laytonsville, MD (Maryland), US (United States of America)
Williams, Taffy J., Lansdale, PA (Pennsylvania), US (United States of America)
Lee, Che-Hung, Silver Spring, MD (Maryland), US (United States of America)
ASSIGNEE(s): The United States of America as represented by the Secretary of the Navy, (A U.S. Government Agency), Washington, DC (District of Columbia, US (United States of America)
[Assignee Code(s): 86584]
EXTRA INFO: Assignment transaction [Reassigned], recorded June 10, 1997 (19970610)
APPL. NO.: 8-137,701
FILED: October 12, 1993 (19931012)

RELATED APPLICATION

This application is a Continuation-in-Part of application 07-918,256, filed 24 Jul. 1992, now abandoned.

FULL TEXT: 1247 lines

8/3/38 (Item 38 from file: 654)
DIALOG(R)File 654:US Pat.Full.

02359526

Utility
ENDOTHELIAL CELL-LEUKOCYTE ADHESION MOLECULES (ELAMS) AND MOLECULES INVOLVED IN LEUKOCYTE ADHESION (MILAS)
[For prevention and treatment of vascular system inflammation by inhibition of leukocyte binding]

PATENT NO.: 5,367,056
ISSUED: November 22, 1994 (19941122)
INVENTOR(s): Hession, Catherine A., South Weymouth, MA (Massachusettes), US (United States of America)
Lobb, Roy R., Westwood, MA (Massachusettes), US (United States of America)
Goelz, Susan E., Winchester, MA (Massachusettes), US (United States of America)
Osborn, Laurelee, Brighton, MA (Massachusettes), US (United States of America)
Benjamin, Christopher D., Beverly, MA (Massachusettes), US (United States of America)
Rosa, Margaret D., Winchester, MA (Massachusettes), US (United States of America)
ASSIGNEE(s): Biogen, Inc, (A U.S. Company or Corporation), Cambridge, MA (Massachusetts), US (United States of America)
[Assignee Code(s): 21695]
APPL. NO.: 8-35,674
FILED: March 23, 1993 (19930323)

This application is a divisional of Ser. No. 07-452,675, filed Dec. 18, 1989, now U.S. Pat. No. 5,272,263, which is a continuation-in-part of Ser. No. 07-359,516, filed Jun. 1, 1989, now abandoned, which is a continuation-in-part of Ser. No. 07,345,151, filed Apr. 28, 1989, now U.S. Pat. No. 5,217,870.

FULL TEXT: 2152 lines

8/3/39 (Item 39 from file: 654)
DIALOG(R)File 654:US Pat.Full.

02254407

Utility
DNA SEQUENCES ENCODING VASCULAR CELL ADHESION MOLECULES (VCAMS)

PATENT NO.: 5,272,263
ISSUED: December 21, 1993 (19931221)
INVENTOR(s): Hession, Catherine A., South Weymouth, MA (Massachusettes), US (United States of America)
Lobb, Roy R., Westwood, MA (Massachusettes), US (United States of America)
Goelz, Susan E., Winchester, MA (Massachusettes), US (United States of America)
Osborn, Laurelee, Brighton, MA (Massachusettes), US (United

States of America)
Benjamin, Christopher D., Beverly, MA (Massachusettes), US (United States of America)
Rosa, Margaret D., Winchester, MA (Massachusettes), US (United States of America)
ASSIGNEE(s): Biogen, Inc , (A U.S. Company or Corporation), Cambridge, MA (Massachusettes), US (United States of America)
[Assignee Code(s): 21695]
APPL. NO.: 7-452,675
FILED: December 18, 1989 (19891218)

This application is a continuation-in-part of copending application Ser. No. 359,516 filed Jun. 1, 1989, now abandoned, which is a continuation-in-part of copending application Ser. No. 345,151 filed Apr. 28, 1989.

FULL TEXT: 2244 lines

t s8/3/1,6,18,24,32,33,38,39,

8/3/1 (Item 1 from file: 654)
DIALOG(R)File 654:US Pat.Full.

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Utility
INHIBITORS OF LEUKOCYTE ADHESION

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ISSUED: December 14, 1999 (19991214)
INVENTOR(s): Thorsett, Eugene D., Moss Beach, CA (California), US (United States of America)
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Pleiss, Michael A., Fremont, CA (California), US (United States of America)
ASSIGNEE(s): Elan Pharmaceuticals, Inc , (A U.S. Company or Corporation), South San Francisco, CA (California), US (United States of America)
APPL. NO.: 8-467,580
FILED: June 06, 1995 (19950606)

This application is a continuation-in-part of U.S. patent application Ser. No. 08-273,055 filed July 11, 1994, now abandoned, which application is incorporated herein by reference in its entirety.

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Utility
METHODS AND COMPOSITIONS FOR TARGETING SELECTINS

PATENT NO.: 5,962,424
ISSUED: October 05, 1999 (19991005)
INVENTOR(s): Hallahan, Dennis E., Park Ridge, IL (Illinois), US (United States of America)
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[Assignee Code(s): 20681]
APPL. NO.: 8-392,541
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The U.S. Government owns rights in the present invention pursuant to grant number 58508 from the National Institutes of Health.

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Williams, Taffy J., Lansdale, PA (Pennsylvania), US (United States of America)
Lee, Che-Hung, Silver Spring, MD (Maryland), US (United States of America)
ASSIGNEE(s): The United States of America as represented by the Secretary of the Navy, (A U.S. Government Agency), Washington, DC (District of Columbia, US (United States of America)
[Assignee Code(s): 86584]
EXTRA INFO: Assignment transaction [Reassigned], recorded June 10, 1997 (19970610)
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RELATED APPLICATION

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PATENT NO.: 5,367,056
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Goelz, Susan E., Winchester, MA (Massachusettes), US (United States of America)
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Benjamin, Christopher D., Beverly, MA (Massachusettes), US (United States of America)
Rosa, Margaret D., Winchester, MA (Massachusettes), US (United States of America)
ASSIGNEE(s): Biogen, Inc, (A U.S. Company or Corporation), Cambridge, MA (Massachusetts), US (United States of America)
[Assignee Code(s): 21695]
APPL. NO.: 8-35,674
FILED: March 23, 1993 (19930323)

This application is a divisional of Ser. No. 07-452,675, filed Dec. 18, 1989, now U.S. Pat. No. 5,272,263, which is a continuation-in-part of Ser. No. 07-359,516, filed Jun. 1, 1989, now abandoned, which is a continuation-in-part of Ser. No. 07,345,151, filed Apr. 28, 1989, now U.S. Pat. No. 5,217,870.

FULL TEXT: 2152 lines

8/3/39 (Item 39 from file: 654)
DIALOG(R)File 654:US Pat.Full.

02254407

Utility
DNA SEQUENCES ENCODING VASCULAR CELL ADHESION MOLECULES (VCAMS)

PATENT NO.: 5,272,263
ISSUED: December 21, 1993 (19931221)
INVENTOR(s): Hession, Catherine A., South Weymouth, MA (Massachusettes), US (United States of America)
Lobb, Roy R., Westwood, MA (Massachusettes), US (United States of America)
Goelz, Susan E., Winchester, MA (Massachusettes), US (United States of America)
Osborn, Laurelee, Brighton, MA (Massachusettes), US (United

States of America)
Benjamin, Christopher D., Beverly, MA (Massachusettes), US (United States of America)
Rosa, Margaret D., Winchester, MA (Massachusettes), US (United States of America)
ASSIGNEE(s): Biogen, Inc , (A U.S. Company or Corporation), Cambridge, MA (Massachusettes), US (United States of America)
[Assignee Code(s): 21695]
APPL. NO.: 7-452,675
FILED: December 18, 1989 (19891218)

This application is a continuation-in-part of copending application Ser. No. 359,516 filed Jun. 1, 1989, now abandoned, which is a continuation-in-part of copending application Ser. No. 345,151 filed Apr. 28, 1989.

FULL TEXT: 2244 lines

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 s vla(w)4 and viral(w)encephalitis

          5509  VLA
       4522487  4
          3338  VLA(W)4
        516031  VIRAL
         48253  ENCEPHALITIS
          1557  VIRAL(W)ENCEPHALITIS
     S7      3  VLA(W)4 AND VIRAL(W)ENCEPHALITIS
? rd s7

...completed examining records
     S8      1  RD S7 (unique items)
? t s8/7/all


 8/7/1     (Item 1 from file: 5)
DIALOG(R)File   5:Biosis Previews(R)
(c) 1999 BIOSIS. All rts. reserv.

10386691   BIOSIS NO.: 199699007836
Regulation of lymphocyte homing into the brain during viral
  encephalitis at various stages of infection.
AUTHOR: Irani David N(a); Griffin Diana E
AUTHOR ADDRESS: (a)Dep. Neurol., Johns Hopkins Hosp., Meyer 6-181, 600 N.
  Wolfe St., Baltimore, MD 21287-7681**USA
JOURNAL: Journal of Immunology  156 (10):p3850-3857 1996
ISSN: 0022-1767
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: The passage of circulating lymphocytes into the central nervous
  system (CNS) during acute viral encephalitis was studied in
  vivo using fluorescently labeled cells inoculated into Sindbis virus
  (SV)-infected mice. Donor lymphocytes were detected in the brains of
  recipient animals when mononuclear cells were isolated from the CNS and
  screened by flow cytometry. The magnitude of this accumulation related to
  the duration of encephalitis in recipient mice and to the activation
  state of the inoculated cells. While Ag specificity did not influence
  lymphocyte entry into the inflamed CNS at any stage of infection,
  SV-immune cells were retained selectively within the brains of infected
  animals compared with cells of an irrelevant specificity. Coincident with
  the onset of CNS inflammation, ICAM-1 and VCAM-1 were up-regulated on
  cerebrovascular endothelium. Lymphocyte entry into the brains of infected
  animals during maximal inflammation could be inhibited by pretreating
  inoculated cells with Abs that blocked LFA-1, but not with those that
  blocked VLA-4 or down-regulated CD44. None of these reagents
  prevented lymphocyte entry into the brain at the onset of inflammation,
  suggesting that the earliest recruited cells utilize presently
  uncharacterized receptor-ligand interactions. These data show that the
  degree of existing inflammation and the activation state of circulating
  cells, but not their Ag specificity, influence lymphocyte recruitment
  into the brain during SV encephalitis. While CNS homing can be blocked
  with Abs against known adhesion molecules during peak inflammation,
  lymphocyte entry into the brain during early infection remains poorly
  characterized.
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ds

Set	Items	Description
S1	108	E1-E11
S2	8	S1 AND (VLA(W)4)
S3	5	RD S2 (unique items)
S4	1	VLA(W)4 AND HERPES
S5	2	VLA(W)4 AND ARBOVIRUS
S6	2	RD S5 (unique items)
S7	3	VLA(W)4 AND VIRAL(W)ENCEPHALITIS

4/7/1 (Item 1 from file: 357)
DIALOG(R)File 357:Derwent Biotechnology Abs

0192337 DBA Accession No.: 96-02530 PATENT
New 3'-derivatized oligonucleotide derivative - oligonucleotide analog for use as a DNA probe or in antisense, triple helix or ribozyme therapy
AUTHOR: Peyman A; Uhlmann E; Carolus C
CORPORATE SOURCE: Frankfurt am Main, Germany.
PATENT ASSIGNEE: Hoechst 1995
PATENT NUMBER: EP 688784 PATENT DATE: 951227 WPI ACCESSION NO.: 96-041520 (9605)
PRIORITY APPLIC. NO.: DE 4424263 APPLIC. DATE: 940709
NATIONAL APPLIC. NO.: EP 95108896 APPLIC. DATE: 950609
LANGUAGE: German
ABSTRACT: A new oligonucleotide analog has specified chemical structure (with numerous specified substituents), and may be linked (3' or 5') to a group which enhances intracellular uptake, serves as a DNA probe label or binds to, crosslinks with or cleaves a target nucleic acid after hybridization. The oligonucleotide analog may be used to inhibit gene expression (as an antisense oligonucleotide, a ribozyme, a sense oligonucleotide or a triple helix-forming oligonucleotide), as a pharmaceutical, as a DNA probe for nucleic acid detection, or as a research tool in molecular biology. The oligonucleotide analog may be used (not claimed) in therapy of viral disease, e.g. caused by HIV virus, **herpes** simplex virus-1, **herpes** simplex virus-2, vesicular-stomatitis virus, influenza virus, hepatitis B virus or papilloma virus, cancer, conditions influenced by integrin or an adhesion receptor (e.g. **VLA-4** , VLA-2, intercellular adhesion molecule or endothelial leukocyte adhesion molecule ELAM-1. They may also be used to prevent restenosis. The analogs show high

s8/k/1,6,18,24,32,33,38,39,

8/K/1 (Item 1 from file: 654)
DIALOG(R)File 654:(c) format only 1999 The Dialog Corp. All rts. reserv.

ABSTRACT

This invention provides peptides which block cellular adhesion mediated by **VLA-4** . The peptides can be used to treat a number of inflammatory diseases, in particular, inflammatory...
... invention to promote adhesion of Jurkat cells in the presence and absence of an anti-**VLA-4** antibody.

FIG. 2 shows the results of experiments demonstrating the ability of peptides of the...
... inhibitors of leukocyte adhesion. In particular, it relates to oligopeptides that block adhesion mediated by **VLA-4**.

REFERENCES

The following publications, patents and patent applications are cited in this application as superscript... and individually indicated to be incorporated by reference in its entirety.

State of the Art

VLA-4 (also referred to as alpha a4 beta 1 integrin and CD49d/CD29), first identified by...

... surface receptors, each of which comprises two subunits, an alpha chain and a beta chain. **VLA-4** contains an alpha 4 chain and a beta 1 chain. There are at least ...a different complement of the various cell matrix molecules, such as fibronectin, laminin, and collagen. **VLA-4**, for example, binds to fibronectin. **VLA-4** is unique among al integrins in that it also binds non-matrix molecules that are...

... is expressed on cytokine-activated human umbilical vein endothelial cells in culture. Distinct epitopes of **VLA-4** are responsible for the fibronectin and VCAM-1 binding activities and each activity has been shown to be inhibited independently. sup 2

Intercellular adhesion mediated by **VLA-4** and other cell surface receptors is associated with a number of inflammatory responses. At the... acid residues, preferably from about 6 to about 10, which inhibit cellular adhesion mediated by **VLA-4**, for example, binding of VCAM-1 to **VLA-4** . The peptides may be either monomeric or dimeric and comprise peptides having a binding affinity to **VLA-4** as expressed by an IC sub 50 of about 50 mu M or less (measured...
...OF THE PREFERRED EMBODIMENTS

This invention provides oligopeptides which comprise adhesion signal sequences recognized by **VLA-4**. Thus, the peptides can be used to block **VLA-4**-mediated adhesion and inhibit immunopathologies associated with this adhesion.

The invention is based, in part, upon sequence analysis of 5 monoclonal antibodies against alpha 4 integrin that inhibit **VLA-4** binding to VCAM-1. This analysis revealed a short consensus stretch of amino acids within...

... other regions of domain 1 of VCAM-1 also block interaction between VCAM-1 and **VLA-4**. One example of a known adhesion signal from domain 1 is QIDS (Vonderheide, et al., ...The peptides of the invention thus comprise sequences derived from the sequences of the anti-**VLA-4** antibodies noted above or from domains of VCAM-1. These sequences present adhesion signals which allow the peptides to inhibit **VLA-4** mediated adhesion in vivo, for instance by binding **VLA-4** thereby disrupting the binding of **VLA-4** to VCAM-1. Preferred adhesion signal sequences are derived from the sequences YYGN (SEQ ID...
... analogs, when appropriately presented, inhibit the binding of protein VCAM-1 to cells that express **VLA-4**, as demonstrated below.

The affinity of the peptides of the invention for the **VLA-4** binding site related to VCAM-1 binding may be determined using the assay described in... in the Example section, below, so long as the subject peptides are able to bind **VLA-4** and inhibit intercellular adhesion. Thus, one of skill will recognize that a number of conservative ... certain functional attributes which are sought (e.g., hydrophobicity versus hydrophilicity). Increased binding affinity for **VLA-4** may also be achieved by such substitutions, compared to the affinity of the parent peptide...example, a compound can be immobilized on a solid surface and adhesion of cells expressing **VLA-4** can be measured. Using such formats, large numbers of specific modifications, (e.g., substitutions, deletions...

... additions) can be screened. Cells suitable for this assay include any leukocytes known to express **VLA-4** such as T cells, B cells, monocytes, and eosinophils, basophils. A number of leukocyte cell...

... The test compounds can also be tested for the ability to competitively inhibit binding between **VLA-4** and VCAM-1, or between **VLA-4** and a labelled compound known to bind **VLA-4**, such as peptides of the invention or antibodies to **VLA-4**. In these assays the VCAM-1 can be immobilized on a solid surface. Alternatively, VCAM... include diagnostic applications such as monitoring inflammatory responses by detecting the presence of leukocytes expressing **VLA-4** . The peptides can also be used for isolating or labeling such cells. In addition, as...

... above, the peptides of the invention can be used to assay for potential inhibitors of **VLA-4**/VCAM-1 interactions.

For in vivo diagnostic imaging to identify, e.g., sites of inflammation ... an inflammatory response in an individual. By measuring the increase or decrease in lymphocytes expressing **VLA-4** it is possible to determine whether a particular therapeutic regimen aimed at ameliorating the disease meningitis and **encephalitis**.

Pharmaceutical compositions of the invention are suitable for use in a variety of drug delivery... demonstrates that a peptide derived from the antibody 21/6 CDR3 region interacts specifically with **VLA-4** integrin.
The peptide used in this example was synthesized based on the sequence of ... derived from the antibody 21/6 CDR3 region can be used as competitive inhibitors of **VLA-4** integrin interaction with VCAM-1.

VCAM-1 was expressed as a soluble fusion protein. The...

...antibody directed against the construct's human IgG tail as a marker.

The activity of **VLA-4** can be regulated. 15/7 is a monoclonal antibody that recognizes an activated conformation of **VLA-4** and locks the molecule in the active state, thereby enhancing **VLA-4** -mediated cell adhesion. 15/7 stabilizes the interaction of Jurkat cells

with the soluble VCAM...

... and 15/7, the soluble VCAM-1 construct interacted with the cell surface in an **VLA-4** -dependent fashion; the interaction was inhibited completely by anti- alpha 4 integrin (21/6), but...derived from the first domain of VCAM-1 can be used as competitive inhibitors of **VLA-4** interaction with VCAM-1.

Peptides derived from the FGN region of VCAM-1 described above...has previously been identified sup 41 as important for the interaction of VCAM-1 with **VLA-4** integrin. A cyclic peptide derived from this sequence was more active than the linear peptide...
What is claimed is:

1. A **VLA-4** binding peptide, comprising
a peptide having 10 or fewer amino acids which includes the sequence YYGN (SEQ ID NO: 158),
wherein said peptide has a binding affinity to **VLA-4**, as evidenced by an IC sub 50 of less than about 50 mu M for inhibiting binding between **VLA-4** and VCAM-1.

2. A pharmaceutical composition comprising a pharmaceutically acceptable carrier and a therapeutically the adhesion of leukocytes mediated by **VLA-4** which method comprises contacting the cells with a composition comprising a peptide of claim 1.

8. The peptide of claim 1, wherein said binding affinity to **VLA-4** is evidenced by an 1C sub 50 that is less than an IC sub 50... selected from the group consisting of hydrogen, lower alkyl, cycloalkyl, aryl and arylalkyl.

12. A **VLA-4** binding ...includes the sequence SEQ ID NO: 163,
wherein said peptide has a binding affinity to **VLA-4**, as evidenced by an IC sub 50 of less than about 50 mu M for inhibiting binding between **VLA-4** and VCAM-1.

13. The peptide of claim 2, wherein said peptide is selected from...

8/K/6 (Item 6 from file: 654)

OTHER REFERENCES

...28):19088-19094, 1991.

Chou and Roizman, "The g sub 1 34.5 Gene of **Herpes** Simplex Virus 1 Precludes Neuroblastoma Cells from Triggering Total Shutoff of Protein Synthesis Characteristic of...

...be employed.

Further suitable E-selectin or L-selectin targeting components are viruses, such as **herpes** simplex virus-1 (HSV-1), adeno-associated virus (AAV), retroviruses, human papilloma virus (HPV) and...of converting a non-toxic pro-drug into a cytotoxic drug. Effective examples include the **herpes** simplex virus (HSV) thymidine kinase (tk) enzyme and the cytosine deaminase enzyme.

The recombinant vector...
... converting a non-toxic pro-drug into a cytotoxic drug. Examples of this are the **herpes** simplex virus (HSV) thymidine kinase (tk) enzyme and the cytosine deaminase enzyme.

The vectors may...could potentially limit intimal expansion. This problem was approached by introducing adenoviral vectors encoding the **herpes**

02877897

Utility

HUMANIZED ANTIBODIES AGAINST LEUKOCYTE ADHESION MOLECULE **VLA-4**
[Binding and treatment of multiple sclerosis]

PATENT NO.: 5,840,299
ISSUED: November 24, 1998 (19981124)
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Leger, Olivier J., Hertfordshire, GB (United Kingdom)
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[Assignee Code(s): 33043]
APPL. NO.: 8-561,521
FILED: November 21, 1995 (19951121)

CROSSREFERENCE TO RELATED APPLICATIONS

This application is a continuation-in-part of PCT-US95-01219, filed Jan. 25, 1995, which is a continuation-in-part of U.S. Ser. No. 08-186,269, (now abandoned) filed Jan. 25, 1994, both of which are incorporated by reference in their entirety for all purposes.

virus thymidine kinase (tk) into porcine arteries that had been injured by a balloon on... migration across monolayers of cytokine-activated endothelial cells: the contribution of CD18, ELAM-1, and **VLA-4** ," Blood, 78(10):2721-6, 1991.
Hallahan et al., "Increased tumor necrosis factor alpha mRNA...
...into a cytotoxic drug.

22. The method of claim 21, wherein said protein is a **herpes** simplex virus (HSV) thymidine kinase (tk) or cytosine deaminase.

23. The method claim 18, wherein...

8/K/18 (Item 18 from file: 654)
DIALOG(R)File 654:(c) format only 1999 The Dialog Corp. All rts. reserv.

... used together. The combination of 130 K/130 P also completely inhibits the interaction of **VLA-4** and VCAM-1 which suggested that alpha sub d and **VLA-4** bind to distinct sites on VCAM-1 and ... neutrophils, unlike their human counterparts, express the T helper cell marker CD4, and also integrin **VLA-4**, and therefore may have different ligands and functions in the dog than in the human...

8/K/24 (Item 24 from file: 654)
DIALOG(R)File 654:(c) format only 1999 The Dialog Corp. All rts. reserv.

OTHER REFERENCES

...specific lymphocyte homing receptor as an integrin molecule with an alpha chain homologous to human **VLA-4** alpha " sub -- Cell 56:37-46 (1989).

Hurtley and Helenius, "Protein oligomerization in the endoplasmic...

... the fusion recipient, including bacterial polypeptides such as trpLE, beta-galactosidase, viral polypeptides such as **herpes** gD protein, and the like. Immunogenic fusions are produced by cross-linking in vitro or... and may include bacterial yeast, mammalian and viral sequences. The native MSP signal or the **herpes** gD glycoprotein signal is suitable for use in mammalian expression systems.

Plasma proteins which have...

8/K/32 (Item 32 from file: 654)
DIALOG(R)File 654:(c) format only 1999 The Dialog Corp. All rts. reserv.

OTHER REFERENCES

... vascular cell adhesion molecule 1 and fibronectin comparison of alpha sup 4 beta sub 1 (**VLA-4**) and alpha sup 4 beta sub 7 on the human B cell line JY, J. Biol. Chem. 267:8366-8370.

Hemler, et al., 1987, Characterization of the cell surface heterodimer **VLA-4** and related peptides, J. Biol. Chem. 262:11478-11485.

Elices, et al., 1990, VCAM-1 on activated endothelium interacts with the leukocyte integrin **VLA-4** at a site distinct from the **VLA-4**/fibronectin binding site, Cell 60:577-584.

Shimizu, et al., 1990, Regulated expression and binding...138(5):1510-1514.

Miyake et al., 1991, Evidence for a role of the Integrin **VLA-4** in lympho-hemopoiesis. J. Exp. Med. 173:599-607.

Williams et al., 1991, Fibronectin and **VLA-4** in haematopoietic stem cell-microenvironment interactions. Nature 352:438-441. Miyake et al., 1991, A...

...3):557-565.

Ryan et al., 1991, Vascular cell adhesion molecule-1 and the integrin **VLA-4** mediate adhesion of human B cell precursors to cultured bone marrow adherent cells, J. Clin...

... Freeman et al., 1990, Adhesion of human B cells to germinal centers in vitro involves **VLA-4** and INCAM-110. Science 249:1030-1033.

Taichman et al., 1991, Tumor cell surface alpha...

... Functional evidence for three distinct and independently inhibitable adhesion activities mediated by the human integrin **VLA-4**. J. Biol. Chem. 266(16):10241-10245.

...

ABSTRACT

... directed to a method for isolating a novel receptor for alpha 4 integrins such as **VLA-4**, that is distinct from VCAM-1 and from fibronectin. Isolated nucleic acids encoding the receptor...

... and methods of treating disorders involving an undesirable inflammatory or immune response by administering the **VLA-4** receptor of the invention.
...b, TS1/22 (anti-LFA-1); c, TS1/22 (anti-LFA-1) +HP2/1 (anti-**VLA-4**); d, TS1/22 (anti-LFA-1)+4B9 (anti-VCAM-1); e, TS1/22 (anti-LFA...

... in quadruplicate. a, control medium; b, TS1/22 (anti-LFA-1); c, HP2/1 (anti-**VLA-4**); d, goat anti-fibronectin; e, To BSA.

FIG. 3B: Ramos and SKW3 cell binding to...

... performed in quadruplicate. a, control medium; b, TS1/22 (anti-LFA-1)+HP2/1 (anti-**VLA-4**); c, TS1/22 (anti-LFA-1)+4B9 (anti-VCAM-1); d, TS1/22 (anti-LFA...
...anti-LFA-1)+E1/6 (anti-VCAM-1)+goat anti-fibronectin.

FIG. 4: Comparison of **VLA-4** -dependent vs. VLA-dependent/E1/6-dependent adhesion of Ramos cells to HUVEC as functions ...

... raw data on which these calculations were based are also shown +- 1 SD. Closed circles, **VLA-4**-dependent; open squares, **VLA-4**-dependent/E1/6-dependent.
...DEMONSTRATION OF THERAPEUTIC UTILITY
5.9.2. THERAPEUTIC ADMINISTRATION AND COMPOSITIONS

6. LYMPHOCYTE ADHESION THROUGH **VLA-4** : EVIDENCE FOR AN ADDITIONAL alpha 4 INTEGRIN COUNTER-RECEPTOR ON STIMULATED ENDOTHELIUM
6.1. MATERIALS...

...HUVEC ADHESION ASSAY
6.1.4. FIBRONECTIN ADHESION ASSAY
6.2. RESULTS
6.2.1. **VLA-4**-DEPENDENT ADHESION OF LYMPHOCYTIC CELL LINES TO TNF-STIMULATED AND UNSTIMULATED HUVEC
6.2.2...
...ENDOTHELIUM DISTINCT FROM VCAM-1 AND FIBRONECTIN
6.2.3. INDUCTION OF E1/6-DEPENDENT/**VLA-4**-DEPENDENT RAMOS CELL ADHESION TO TNF-STIMULATED HUVEC

6.3. DISCUSSION

7. FUNCTIONAL CLONING OF THE **VLA-4** RECEPTOR
7.1. PANNING METHOD
7.2. ROSETTE METHOD
7.3. SUBPOOL SELECTION

8. PRODUCTION...

...1. INTRODUCTION

The present invention relates to a receptor for alpha 4 integrins such as **VLA-4** , that is distinct from VCAM-1 and fibronectin, and therapeutic uses of such receptor.

2...

... surface heterodimers--lymphocyte function-associated antigen-1 (LFA-1) and very late activation antigen-4 (**VLA-4**)--mediate distinct mechanisms for lymphocyte-endothelial cell adhesion. LFA-1, whose expression is limited to...

... Annu. Rev. Immunol. 5:223; Carlos and Harlan, 1990, Immunol. Rev. 114:1).

The integrin **VLA-4**, that contains the alpha 4 (CD49d) subunit noncovalently associated with the beta 1 (CD29) subunit...at least 48 hr (Carlos et al., 1990, Blood 76:965). Unlike LFA-1, however, **VLA-4** can also interact with fibronectin, binding to the alternatively spliced CS-1 region located C...

... et al., 1989, J. Cell Biol. 109:1321; Hemler, 1990, Annu. Rev. Immunol. 8:365). **VLA-4** and its counter-receptors have been implicated in a number of physiologic and pathophysiologic processes...

... 1989, Nature 339:61; de Fougerolles and Springer, 1991, J. Exp. Med. In press). Although **VLA-4** has been shown to bind to fibronectin and VCAM-1, it has not been known whether **VLA-4** interacts with other ligand(s) completely distinct from VCAM-1.

Adhesion to endothelium that is...inhibition between the anti-VCAM-1 mAb 4 beta 9 and a function-blocking anti-**VLA-4** mAb (Oppenheimer-Marks et al., 1991, J. Immunol. 147:2913). In a study (Schwartz et...

... 4B9 failed to inhibit binding to stimulated HUVEC as well as a function-blocking anti-**VLA-4** mAb; the difference was attributed to lymphocyte interactions with fibronectin on HUVEC. In studies (Graber...

... herein shall mean molecules comprising the alpha 4 integrin subunit, including but not limited to **VLA-4** (alpha 4 beta 1), alpha 4 beta 7, and the alpha 4 subunit itself. Isolated...

... and methods of treating disorders involving an undesirable inflammatory or immune response by administering the **VLA-4** receptor of the invention.

3.1. DEFINITIONS

As used herein, the following terms shall have...

...Ig domain form of VCAM-1.
VCAM-7D, seven Ig domain form of VCAM-1.

VLA-4, very late activation antigen-4.
... herein shall mean molecules comprising the alpha 4 integrin subunit,

including but not limited to **VLA-4** (an alpha 4 beta 1 heterodimer), alpha 4 beta 7 (Chan et al., 1992, J...

... lymphoid cell lines to stimulated and unstimulated HUVEC and compared the inhibitory effects of anti-**VLA-4** and anti-VCAM-1 mAb. Anti-fibronectin antiserum was also studied to assess the role...

... with a cDNA library (preferably synthesized from stimulated endothelial cell mRNA), incubating the cells in **VLA-4** coated plastic dishes with an anti-VCAM-1 mAb that blocks binding of **VLA-4** to VCAM-1 and preferably also with an anti-fibronectin antiserum that blocks binding of **VLA-4** to fibronectin, and recovering plasmid from adherent cells. The cDNA can be expressed to produce...that, e.g., has similar or identical electrophoretic migration, isolectric focusing behavior, proteolytic digestion maps, **VLA-4** or other alpha 4 integrin binding activity, or antigenic properties as known for the Receptor...

... represent available, purified Receptor DNA of another species. Immunoprecipitation analysis or functional assays (e.g., **VLA-4** binding ability in vitro) of the in vitro translation products of the isolated products of... synthetic techniques and in vivo recombinants (genetic recombination). Expression of nucleic acid sequence encoding the **VLA-4** Receptor or fragment thereof may be regulated by a second nucleic acid sequence so that... terminal repeat of Rous sarcoma virus (Yamamoto, et al., 1980, Cell 22:787-797), the **herpes** thymidine kinase promoter (Wagner et al., 1981, Proc. Natl. Acad. Sci. U.S.A. 78 binding to **VLA-4** , binding to alpha 4 beta 7, binding with antibody.

Once a particular recombinant DNA molecule...Such molecules which retain, or alternatively inhibit, a desired Receptor property, e.g., binding to **VLA-4** or other ligand having an alpha 4 integrin subunit, can be used as inducers, or...invention.

In another embodiment, where one is assaying for the ability to mediate binding to **VLA-4** or the alpha 4 integrin subunit, one can carry out an in vitro binding assay...

... of lymphoid cell line to HUVEC, or assay directly for the ability to bind to **VLA-4** coated on plastic dishes.

5.7. GENERATION AND USE OF ANTIBODIES TO THE .alpha.4...

... Fab fragments, and an Fab expression library. In a specific embodiment, antibodies to the human **VLA-4** Receptor are produced. In another embodiment, antibodies to the extracellular domain of the Receptor are... the ability of their secreted antibodies to inhibit binding of stimulated endothelial cells to purified **VLA-4** (and/or other purified alpha 4 integrin(s)) coated on a solid phase surface such as plastic, in the presence of an anti-VCAM-1 mAb that blocks binding of **VLA-4** (or the other alpha 4 integrin) to VCAM.-1, and preferably also in the presence of an anti-fibronectin antiserum that blocks binding of **VLA-4** (or the other alpha 4 integrin) to fibronectin. An antibody with such ability is selected...

... inhibit binding of cells (e.g., transfected COS cells) expressing a Receptor cDNA to purified **VLA-4** (or other alpha 4 integrin) coated on a solid phase surface such as plastic. An...

... endothelial cells in the presence of an anti-VCAM-1 mAb that blocks binding of **VLA-4** to VCAM-1, and preferably also in the presence of an antiserum to fibronectin that blocks binding of **VLA-4** to fibronectin. If the lymphoid cells (e.g., Ramos, SKW3) express LFA-1, the screening...

... molecule is screened for the ability to inhibit stimulated endothelial

cells from binding to purified **VLA-4** (and/or other purified alpha 4 integrin(s)) on a solid surface such as plastic, in the presence of an anti-VCAM-1 mAb that blocks binding of **VLA-4** (or the other alpha 4 integrin) to VCAM-1, and preferably also in the presence of an antiserum to fibronectin that blocks binding of **VLA-4** (or the other alpha 4 integrin) to fibronectin.

In another embodiment, a molecule is screened...

... inhibit cells (e.g., transfected COS cells) expressing a Receptor cDNA from binding to purified **VLA-4** (and/or other purified alpha 4 integrin(s)) on a solid surface such as plastic... by the agency of manufacture, use or sale for human administration.

6. LYMPHOCYTE ADHESION THROUGH **VLA-4** : EVIDENCE FOR AN ADDITIONAL .alpha.4 INTEGRIN COUNTER-RECEPTOR ON STIMULATED ENDOTHELIUM

We compared the inhibitory effects of anti-VCAM-1 and anti-**VLA-4** mAbs on lymphoid cell adhesion to cultured human umbilical vein endothelial cells (HUVEC). The anti...to stimulated HUVEC better than the anti-VCAM-1 mAb E1/6. Although the anti-**VLA-4** mAb and anti-VCAM-1 mAb 4B9 equally inhibited PBL binding to stimulated HUVEC, mAb 4B9 inhibited the binding of two lymphoid cell lines significantly less than anti-**VLA-4** mAb. Combination of 4B9 mAb with function blocking antiserum to human fibronectin, a second known ligand for **VLA-4**, also failed to inhibit as much as anti-**VLA-4** mAb. These findings suggest that adhesion of lymphoid cell lines through **VLA-4** or other alpha 4 integrins involves inducible counter-receptor(s) on endothelium distinct from either...

...et al., 1982, Proc. Natl. Acad. Sci. U.S.A. 79:7489), HP2/1 (anti-**VLA-4**) (Moser et al., 1989, J. Clin. Invest. 83:444), 4B9 (anti-VCAM-1) (Carlos et... percent adherence was determined using a fluorescence concentration analyzer.

6.2. RESULTS

6.2.1. **VLA-4** -DEPENDENT ADHESION OF LYMPHOCYTIC CELL LINES TO TNF-STIMULATED AND UNSTIMULATED HUVEC

The anti-**VLA-4** mAb HP2/1 and the anti-VCAM-1 mAb 4B9 and E1/6 were compared...

... FIG. 2A-2C). When PBL, Ramos or SKW3 cells were pre-incubated with the anti-**VLA-4** mAb HP2/1 in addition to TS1/22, binding to TNF-stimulated HUVEC was significantly...

... in addition to TS1/22, only slight further inhibition in binding was observed, indicating that **VLA-4** counter-receptor(s) on endothelium are cytokine inducible. Basal cell line adhesion to unstimulated HUVEC...PBL, bound to stimulated endothelium through a pathway that was blocked by mAb to the **VLA-4** alpha subunit but not by 4B9 mAb to VCAM-1. These mAb completely blocked binding of the same cells to COS cells expressing VCAM-1. Because **VLA-4** can bind to an alternatively spliced form of fibronectin (Guan and Hynes., 1990, Cell 60 ...

... plates with antiserum to human fibronectin (FIG. 3A). Cell line pre-incubation with the anti-**VLA-4** mAb HP2/1 also completely blocked binding to fibronectin whereas preincubation with the anti-LFA...

... determined by flow cytometric analysis (data not shown). This result therefore confirms previous reports of **VLA-4** - dependent/VLA-5-independent adhesion of lymphocytes to fibronectin (Guan and Hynes, 1990, Cell 60...

... was observed (additional inhibition <8%) (FIG. 3B). Inhibition remained

substantially less than that obtained with **VLA-4** mAb. These results suggest that cell lines express an integrin containing the **VLA-4** alpha subunit that can recognize a ligand on stimulated endothelium that is distinct from VCAM-1 and fibronectin.

6.2.3. INDUCTION OF E1/6-DEPENDENT/**VLA-4**-DEPENDENT RAMOS CELL ADHESION TO TNF-STIMULATED HUVEC

To determine the induction of E1/6...

...of TNF stimulation. HUVEC used for any one experiment were from a single umbilical cord. **VLA-4**-dependent adhesion was calculated as the percentage of Ramos cell binding that was blocked by anti-**VLA-4** mAb HP2/1 in the presence of anti-LFA-1 mAb TS1/22. For five experiments, **VLA-4** -dependent adhesion increased as the time of TNF stimulation increased (FIG. 4, Table 1), consistent with the cytokine inducibility of **VLA-4** counter-receptor(s) on endothelium. There was no significant **VLA-4** -dependent adhesion to unstimulated HUVEC.

TABLE 1**VLA-4** -dependent adhesion that could be blocked by E1/6 in the presence of anti-LFA...

...Results from five experiments showed that after 2 hr of TNF stimulation, the majority of **VLA-4** -dependent binding of Ramos cells was E1/6-dependent, but after 7 hr of stimulation, the majority of **VLA-4**-dependent adhesion was not blocked by E1/6 (FIG. 4).

6.3. DISCUSSION

The integrin **VLA-4** mediates lymphocyte adhesion to stimulated endothelium by binding to VCAM-1, a member of the...

...VCAM-7D).

Using the HUVEC system, we directly compared the inhibitory effects of the anti-**VLA-4** mAb HP2/1 and the anti-VCAM-1 mAb 4B9 in order to determine whether there might exist **VLA-4** counter-receptors distinct from VCAM-1. Here, we chose mAb HP2/1 to **VLA-4** alpha and 4B9 to VCAM-1 for comparison because either mAb used alone completely blocks...

... it has been shown that mAb HP2/1 completely blocks two other adhesive functions of **VLA-4**; namely, interactions with fibronectin and lymphocyte homotypic aggregation (Pulido et al., 1991, J. Biol Chem...

... 1 and 4B9 blocked adhesion to stimulated HUVEC equally well, suggesting no use of alternative **VLA-4** counter-receptors; however, for the two cell lines tested, mAb HP2/1 blocked adhesion to...

... a pathway of adhesion of T cell lines to stimulated endothelium that is blocked by **VLA-4** alpha subunit mAb but not VCAM-1 mAb is particularly strong because of our demonstration...

...cells (Erle et al., 1991, J. Biol. Chem. 266:11009).

7. FUNCTIONAL CLONING OF THE **VLA-4** RECEPTOR

7.1. PANNING METHOD

Purified **VLA-4** is coated on plastic, and a modified version of the procedure of Aruffo and Seed 339:61-64) for the cloning of ICAM-2, as detailed below.

VLA-4 is purified from tonsil cell lysates by immunoaffinity chromatography on anti-**VLA-4** mAb Sepharose, and eluted at basic

pH in the presence of 2 mM MgCl sub 2 and 1% octylglucoside. Alternatively, purified **VLA-4** is obtained by recombinant methods by expression from cells transfected with a DNA clone encoding **VLA-4** (Elices et al., 1990, Cell 60:577). **VLA-4** (10 mu g per 200 mu l per 6-cm plate) is bound to bacteriological...

... and panned (Seed and Aruffo, 1987, Proc. Natl. Acad. Sci. USA 84:3365-3369) on **VLA-4** coated plates. The cell suspension is incubated in the **VLA-4** coated plates at 25 degree(s) C. for 1 hour. The transfected COS cells are incubated in the **VLA-4** coated dishes with anti-VCAM-1 and preferably also with anti-fibronectin antibody present to...

... in LB medium, pooled, and plasmid is prepared by the alkal-ilysis method. Selection of **VLA-4**-adherent transfected COS cells and plasmid recovery is repeated twice. Pooled colonies obtained after the...
... different size fractions. Individual plasmids from the fraction with greatest activity in promoting adhesion to **VLA-4** of COS cells transfected with such plasmids are examined for uniqueness by restriction enzyme digestion... eukaroytic cells. The COS cells are incubated with a medium comprising (i) cells of a **VLA-4** (or other alpha 4 integrin)- expressing lymphoid cell line, and (ii) an anti-VCAM-1 mAb that blocks binding of **VLA-4** (or the other alpha 4 integrin) to VCAM-1. In addition, the incubation is preferably also in the presence of an anti-fibronectin antiserum that blocks binding of fibronectin to **VLA-4** (or the other alpha 4 integrin). If the lymphoid cell line expresses LFA-1 (e...

... plastic and incubated with a medium comprising cells of a lymphoid cell line that express **VLA-4** (or other alpha 4 integrin) in the presence of an anti-VCAM-1 mAb such...

... are then cultured on plastic and incubated with a medium comprising (i) cells of a **VLA-4** (or other alpha 4 integrin)-expressing lymphoid cell line, and (ii) an anti-VCAM-1 mAb that blocks binding of **VLA-4** (or the other alpha 4 integrin) to VCAM-1. In addition, the incubation is preferably also in the presence of an anti-fibronectin antiserum that blocks binding of fibronectin to **VLA-4** (or the other alpha 4 integrin). If the lymphoid cell line expresses LFA-1 (e...
...in E. coli.

8. A method for isolating a cDNA molecule encoding a receptor for **VLA-4** or for the **VLA-4** alpha 4 subunit, comprising the following steps in the order stated:
(a) incubating a plastic surface of a dish, said surface coated with purified **VLA-4** , with a medium comprising (i) COS cells transfected with an expression plasmid cDNA library synthesized...

... endothelial cell mRNA, and (ii) a monoclonal antibody to VCAM-1 that blocks binding of **VLA-4** to VCAM-1, for a time period sufficient to allow binding of a transfected cell...

... the medium of step (a) further comprises an antiserum to fibronectin that blocks binding of **VLA-4** to fibronectin.

10. A method for isolating a cDNA molecule encoding a receptor for an...

8/K/33 (Item 33 from file: 654)

...surface molecule which has been demonstrated to mediate intercellular adhesion via interaction with the integrin **VLA-4**, which is expressed on monocytes, lymphocytes, basophils, eosinophils, and certain tumor cells, but not neutrophils...

... Contained within the VCAM-1 molecule are six immunoglobin-like domains which interact with the **VLA-4** receptor on lymphocytes. Several lines of evidence are consistent with an important role for VCAM...

... unstimulated or activated endothelium by disruption of the recognition that occurs between VCAM-1 and **VLA-4**. The use of monoclonal antibodies against either **VLA-4** and/or VCAM-1 can be useful in preventing the recognition of the receptor/ligand...in vivo data has shown that antisense oligonucleotides to 5' viral sequences of tick-borne **encephalitis** virus were capable of providing protection (30-50% survival in treated animals versus 100% lethality...

8/K/38 (Item 38 from file: 654)

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Takada, Y., et al., "The Primary Structure of the alpha sup 4 Subunit of **VLA-4** : Homology to Other Integrins and a Possible Cell-Cell Adhesion Function", EMBO J., 8, pp...

...pp. 3300-09 (1987a)

Hemler, M. E., et al., "Characterization of the Cell Surface Heterodimer **VLA-4** and Related Peptides," J. Biol. Chem., 262, pp. 11478-85 (1987b)

Hirt, B., "Selective Extraction...Harbor, N.Y. (1989)

Sandri-Goldin, R. M., et al., "High Frequency Transfer of Cloned **Herpes** Simplex Virus Type I Sequences to Mammalian Cells by Protoplast Fusion", Molec. and Cell Biol...407 (1989)

Takada, Y., et al., "The Primary Structure of the alpha 4 Subunit of **VLA-4** : Homology to Other Integrins and a Possible Cell-Cell Adhesion Function," EMBO J., 8, pp...

8/K/39 (Item 39 from file: 654)

OTHER REFERENCES

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Hemler, M. E., et al., "Characterization of the Cell Surface Heterodimer **VLA-4** and Related Peptides", J. Biol. Chem., 262, pp. 11478-11485 (1987) (Hemler et al. II...14.2-14.35.

Sandri-Goldin, R. M., et al., "High Frequency Transfer of Cloned **Herpes** Simplex Virus Type I Sequences to Mammalian Cells by Protoplast Fusion", Molec. Cell Biol., 1...407 (1989).

Takada, Y., et al., "The Primary Structure of the sup 4 Subunit of **VLA-4** : Homology to Other Integrins and a Possible Cell-Cell Adhesion Function", EMBO J., 8, pp...

...pp. 3300-09 (1987a)

Hemler, M. E., et al., "Characterization of the Cell Surface Heterodimer **VLA-4** and Related Peptides," J. Biol. Chem., 262, pp. 11478-85 (1987b)

Hirt, B., "Selective Extraction...Harbor, N.Y. (1989)

Sandri-Goldin, R. M., et al., "High Frequency Transfer of Cloned **Herpes** Simplex Virus Type I Sequences to Mammalian Cells by Protoplast Fusion", Molec. and Cell Biol...407 (1989) Takada, Y., et al., "The Primary Structure of the alpha 4 Subunit of **VLA-4**: Homology to Other Integrins and a Possible Cell-Cell Adhesion Function," EMBO J., 8, pp...
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          311261  ADHESION
         1089626  MOLECULE?
           94880  ADHESION(W)MOLECULE?
          108578  HERPES
           45321  ENCEPHALITIS
           28202  ENCEPHALOMYELITIS
      S3      17  (ADHESION(W)MOLECULE?) AND HERPES AND (ENCEPHALITIS OR
                  ENCEPHALOMYELITIS)
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>>>Format 7 is not valid in file 143

 4/7/1     (Item 1 from file: 5)
DIALOG(R)File   5:Biosis Previews(R)
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09684805   BIOSIS NO.: 199598139723
Adhesion molecule expression and lymphocyte adhesion to
  cerebral endothelium: Effects of measles virus and herpes simplex 1
  virus.
AUTHOR: Brankin B(a); Hart M N; Cosby S L; Fabry Z; Allen I V
AUTHOR ADDRESS: (a)Div. Neuropathol., Queen's Univ. Belfast, Inst. Clinical
  Sci., Grosvenor Road, Belfast BT12 6BL**UK
JOURNAL: Journal of Neuroimmunology  56 (1):p1-8 1995
ISSN: 0165-5728
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: Expression of endothelial cell (EC) adhesion
  molecules is increased in inflammatory neurological disorders and
  this may regulate lymphocyte homing to the central nervous system (CNS).
  Viral encephalitis is characterized by lymphocytic infiltration of
  the CNS and one mechanism of this response may be EC adhesion
  molecule induction with consequent inflammatory cell/EC binding.
  This report characterizes the effects of herpes simplex 1 (HSV1) or
  measles virus (MV) infection of BALB/c brain microvascular EC in vitro on
  adhesion of naive syngenic splenocytes and levels of ICAM-1. Adhesion was
  enhanced by 42% for MV-infected cells and by 73% for HSV-1-infected EC.
  At the multiplicities of infection employed, levels of ICAM-1 were
  upregulated on HSV-1-infected EC, but not on MV-infected EC. It is
  concluded that ICAM-1/ligand interactions do not play a role in mediation
  of MV enhancement of adherence, but represent one mechanism responsible
  for increased lymphocyte adherence to HSV-1-infected cerebral EC.


 4/7/2     (Item 2 from file: 5)
DIALOG(R)File   5:Biosis Previews(R)
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06455812   BIOSIS NO.: 000037027823
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INTERCELLULAR **ADHESION MOLECULE**-1 ICAM-1 IN CENTRAL NERVOUS SYSTEM CNS IMMUNOPATHOLOGY
AUTHOR: SOBEL R A; MITCHELL M; ROTHLEIN R
AUTHOR ADDRESS: MASS. GEN. HOSP., HARV. MED. SCH., BOSTON, MASS. 02114.
JOURNAL: 73RD ANNUAL MEETING OF THE FEDERATION OF AMERICAN SOCIETIES FOR EXPERIMENTAL BIOLOGY, NEW ORLEANS, LOUISIANA, USA, MARCH 19-23, 1989. FASEB (FED AM SOC EXP BIOL) J 3 (4). 1989. A1320.
CODEN: FAJOE
DOCUMENT TYPE: Meeting
RECORD TYPE: Citation
LANGUAGE: ENGLISH

4/7/3 (Item 1 from file: 34)
DIALOG(R)File 34:SCISEARCH(R) CITED REF SCI

05949449 Genuine Article#: XJ374 Number of References: 78
Title: Infections with cutaneous and nervous system alterations
Author(s): LosadaCampa A; SeijoMartinez M; delaTorreFraga C
Corporate Source: HOSP PROV PONTEVEDRA,SECC NEUROL/E-36611 PONTEVEDRA//SPAIN/; HOSP PROV PONTEVEDRA,SERV DERMATOL/E-36611 PONTEVEDRA//SPAIN/
Journal: REVISTA DE NEUROLOGIA, 1997, V25, 3 (SEP), PS281-S293
ISSN: 0210-0010 Publication date: 19970900
Publisher: REVISTA DE NEUROLOGIA, C/O CESAR VIGUERA, EDITOR, APDO 94121, 08080 BARCELONA, SPAIN
Language: Spanish Document Type: ARTICLE
Abstract: Objective. We review and update the clinical and diagnostic aspects in the most representative neurocutaneous infections, emphasizing the features of interdisciplinary interest. Methods. Human skin is the primary host barrier against infection and his importance is critical in the immunocompromised population. The genetic hability of pathogen micro-organisms to bind the **adhesion molecules** of cellular membranes defines the anatomic affinity of each species. Cutaneous involvement can be crucial for diagnosis in infectious diseases. The characteristics of the elemental lesions and the accesible citology, bacteriology and histopathology procedures, usually leads to a specific diagnosis. We highlight the cutaneous manifestations of the acute and subacute bacterial meningitides. We review the clinico-pathologic characterisitics of the meningoencefalitidis associated to the viral exanthems. We describe the chronic bacterial entities with prominent cutaneous and neural affectation as lepra, syphilis and borreliosis, as well as the numerous clinical forms of presentation of herpesvirus hominis and varicellazoster. Finally, we stand out the trascendency of cutaneous findings in the VIH set. Conclusions. The appropiate interpretation of the infectious cutaneous semiology, supplemented with exams of direct samples, allow frequently to reach an ethiologic or oriented diagnosis, in a rapid, economic and non-invasive way. This information must be carefully incorporated to the study of high-morbidity infections, as there that concerns to the nervous system.

4/7/4 (Item 2 from file: 34)
DIALOG(R)File 34:SCISEARCH(R) CITED REF SCI

04599677 Genuine Article#: TW031 Number of References: 35
Title: EXPERIMENTAL BRAIN GLIOMA - GROWTH ARREST AND DESTRUCTION BY A BLOOD-GROUP-RELATED TETRASACCHARIDE
Author(s): NIETOSAMPEDRO M; BAILON C; FERNANDEZMAYORALAS A; MARTINLOMAS M; MELLSTROM B; NARANJO JR
Corporate Source: INST CAJAL,CSIC,DEPT NEURAL PLAST,37 AVE DOCTORARCE/E-28002 MADRID//SPAIN/; CSIC,INST ORGAN CHEM,CARBOHYDRATE GRP/E-28006 MADRID//SPAIN/

Journal: JOURNAL OF NEUROPATHOLOGY AND EXPERIMENTAL NEUROLOGY, 1996, V55, N2 (FEB), P169-177
ISSN: 0022-3069
Language: ENGLISH Document Type: ARTICLE
Abstract: A synthetic tetrasaccharide (TSI), structurally related to blood groups, inhibited the proliferation of C6 glioma cells in culture and the growth of tumors formed after intracerebral transplantation of C6 cells. TS4-treated tumors were substantially smaller than controls, as expected from TS4 cytostatic action on C6 glioma cells in culture. However, in vivo treatment also caused extensive tumor destruction. This effect appeared to be caused indirectly, either by activation of natural killer cells, cytotoxic lymphocytes, or by inhibition of tumor vascularization. Enhanced antigenicity of TS4-treated glioma may be related to the increased expression of connexin 43 observed in glioma cell cultures treated with the oligosaccharide. Because concentrations of up to 20 mg/ml of TS4 were not toxic for normal neuronal or glial cells, specific oligosaccharides such as TS4 offer the possibility of selective tumor treatment.

4/7/5 (Item 3 from file: 34)
DIALOG(R)File 34:SCISEARCH(R) CITED REF SCI

04522918 Genuine Article#: TK087 Number of References: 41
Title: CHARACTERISTICS OF CLONED CEREBROVASCULAR ENDOTHELIAL-CELLS FOLLOWING INFECTION WITH THEILERS VIRUS .1. ACUTE INFECTION
Author(s): WELSH CJR; SAPATINO BV; ROSENBAUM BA; SMITH R
Corporate Source: TEXAS A&M UNIV,COLL VET MED,DEPT VET ANAT & PUBL HLTH/COLLEGE STN//TX/77843; TEXAS A&M UNIV,COLL VET MED,DEPT VET PATHOBIOL/COLLEGE STN//TX/77843
Journal: JOURNAL OF NEUROIMMUNOLOGY, 1995, V62, N2 (NOV), P119-125
ISSN: 0165-5728
Language: ENGLISH Document Type: ARTICLE
Abstract: The present study describes the replication of Theiler's virus in cloned cerebrovascular endothelial cells (CVE) isolated from strains of mice that are either susceptible or resistant to Theiler's virus-induced demyelination (TVID). CVE isolated from all strains of mice were equally permissive to Theiler's virus infection. Interferon-gamma and tumor necrosis factor-alpha were found to inhibit the replication of Theiler's virus in CVE. A correlation between susceptibility to demyelination and the ability of Theiler's virus to induce MHC Class I on CVE was demonstrated.

4/7/6 (Item 4 from file: 34)
DIALOG(R)File 34:SCISEARCH(R) CITED REF SCI

04116733 Genuine Article#: BD17U Number of References: 65
Title: PATHOGENETIC MECHANISMS OF POSTPOLIO SYNDROME - MORPHOLOGICAL, ELECTROPHYSIOLOGICAL, VIROLOGICAL, AND IMMUNOLOGICAL CORRELATIONS
Author(s): DALAKAS MC
Corporate Source: NINCDS,MED NEUROL BRANCH,BLDG 10,ROOM 4N248,10 CTR DR,MSC 1382/BETHESDA//MD/20892
Journal: ANNALS OF THE NEW YORK ACADEMY OF SCIENCES, 1995, V753, P167-185
ISSN: 0077-8923
Language: ENGLISH Document Type: ARTICLE

4/7/7 (Item 5 from file: 34)
DIALOG(R)File 34:SCISEARCH(R) CITED REF SCI

03765566 Genuine Article#: QD616 Number of References: 21
Title: INVOLVEMENT OF LFA-1 AND ICAM-1 IN THE HERPETIC DISEASE RESULTING

FROM HSV-1 CORNEAL INFECTION
Author(s): DENNIS RF; SIEMASKO KF; TANG QZ; HENDRICKS RL; FINNEGAN A
Corporate Source: RUSH PRESBYTERIAN ST LUKES MED CTR,DEPT OPHTHALMOL,1753 W CONGRESS PKWY/CHICAGO//IL/60612; RUSH PRESBYTERIAN ST LUKES MED CTR,DEPT IMMUNOLMICROBIOL/CHICAGO//IL/60612; RUSH PRESBYTERIAN ST LUKES MED CTR,DEPT INTERNAL MED,RHEUMATOL SECT/CHICAGO//IL/60612; UNIV ILLINOIS,DEPT MICROBIOL & IMMUNOL/CHICAGO//IL/60680; UNIV ILLINOIS,DEPT OPHTHALMOL & VISUAL SCI/CHICAGO//IL/00000; UNIV ILLINOIS,DEPT PATHOL/CHICAGO//IL/00000
Journal: CURRENT EYE RESEARCH, 1995, V14, N1 (JAN), P55-62
ISSN: 0271-3683
Language: ENGLISH Document Type: ARTICLE
Abstract: **Herpes** simplex virus type 1 (HSV-1) corneal infection in immunologically normal mice results in a transient epithelial lesion followed in about 2 weeks by a potentially blinding inflammatory response in the corneal stroma, and a mild blepharitis. Similarly infected T cell-deficient mice do not develop corneal stromal inflammation, but exhibit severe periocular skin disease and succumb to viral **encephalitis**. The role of certain **adhesion molecules** in both T cell activation, and in the extravasation of inflammatory cells from the blood into inflammatory sites is now being established. These studies investigated the involvement of the adhesion pair LFA-1/ICAM-1 in the disease that results from HSV-1 corneal infection in mice.

Treatment of mice with mAb to LFA-1 beginning 1 day before HSV-1 corneal infection resulted in a delay in the onset of stromal inflammation, but ultimately stromal inflammation developed to a normal extent. This treatment also caused a significant exacerbation of periocular skin disease, but did not render mice susceptible to **encephalitis**. Treatment with mAb to ICAM-1 beginning 1 day before HSV-1 corneal infection caused an acceleration of both stromal inflammation and periocular skin disease, and rendered mice uniformly susceptible to lethal **encephalitis**. Treatment with either mAb beginning 6 days after HSV-1 corneal infection did not significantly affect the clinical course of herpetic disease.

Our findings suggest that LFA-1 may play a role in the early phase of corneal stromal inflammation following HSV-1 corneal infection. Both LFA-1 and ICAM-1 appear to be important for protection of the skin from HSV-1 infection. ICAM-1 but not LFA-1 is necessary for protection from **encephalitis** following corneal infection.

4/7/8 (Item 6 from file: 34)
DIALOG(R)File 34:SCISEARCH(R) CITED REF SCI

03550956 Genuine Article#: PL703 Number of References: 50
Title: EXOGENOUS TAT PROTEIN ACTIVATES CENTRAL NERVOUS SYSTEM-DERIVED ENDOTHELIAL-CELLS
Author(s): HOFMAN FM; DOHADWALA MM; WRIGHT AD; HINTON DR; WALKER SM
Corporate Source: UNIV SO CALIF,SCH MED,DEPT PATHOL,2011 ZONAL AVE/LOS ANGELES//CA/90033; CHILDRENS HOSP,DEPT PEDIAT/LOS ANGELES//CA/90027; UNIV SO CALIF,SCH MED,DEPT MICROBIOL/LOS ANGELES//CA/90033
Journal: JOURNAL OF NEUROIMMUNOLOGY, 1994, V54, N1-2 (OCT), P19-28
ISSN: 0165-5728
Language: ENGLISH Document Type: ARTICLE
Abstract: Tat protein, an HIV gene product known to be secreted extracellularly, was tested to determine its role in the dissemination of HIV into the central nervous system (CNS). Tat was shown to activate human CNS-derived endothelial cells (CNS-EC) by the increase in the expression of E-selectin, the synthesis of IL-6, and the secretion of plasminogen activator inhibitor-1 (PAI-1). Tat also functioned synergistically with tumor necrosis factor alpha (TNF). AIDS brains stained for tat in situ, demonstrated positive cells. These data

suggest that secreted tat protein may increase leukocyte binding, and alter the blood-brain barrier permeability to enhance dissemination of HIV-infected cells into the CNS.

4/7/9 (Item 7 from file: 34)
DIALOG(R)File 34:SCISEARCH(R) CITED REF SCI
(c) 1999 INST FOR SCI INFO. All rts. reserv.

03078057 Genuine Article#: BZ69J Number of References: 514
Title: PATHOGENESIS OF VIRUS-INDUCED DEMYELINATION
Author(s): FAZAKERLEY JK; BUCHMEIER MJ
Corporate Source: UNIV CAMBRIDGE,DEPT PATHOL/CAMBRIDGE CB2 1QP//ENGLAND/; SCRIPPS CLIN & RES INST,DEPT NEUROPHARMACOL,DIVVIROL/LA JOLLA//CA/00000
Journal: ADVANCES IN VIRUS RESEARCH, 1993, V42, P249-324
ISSN: 0065-3527
Language: ENGLISH Document Type: REVIEW

4/7/10 (Item 8 from file: 34)
DIALOG(R)File 34:SCISEARCH(R) CITED REF SCI
(c) 1999 INST FOR SCI INFO. All rts. reserv.

02903014 Genuine Article#: MN277 Number of References: 141
Title: MANAGEMENT OF CEREBRAL INFECTION
Author(s): ANDERSON M
Corporate Source: MIDLAND CTR NEUROSURG & NEUROL,HOLLY LANE/WARLEY B67 7JX/W MIDLANDS/ENGLAND/
Journal: JOURNAL OF NEUROLOGY NEUROSURGERY AND PSYCHIATRY, 1993, V56, N12 (DEC), P1243-1258
ISSN: 0022-3050
Language: ENGLISH Document Type: REVIEW

4/7/11 (Item 9 from file: 34)
DIALOG(R)File 34:SCISEARCH(R) CITED REF SCI
(c) 1999 INST FOR SCI INFO. All rts. reserv.

01870917 Genuine Article#: JH350 Number of References: 147
Title: CAN POLIOVIRUS CAUSE A PERSISTANT INFECTION
Author(s): COLBEREGARAPIN F; BORZAKIAN S; CALVEZ V; PELLETIER I
Corporate Source: INST PASTEUR,UNITE VIROL MED/F-75724 PARIS 15//FRANCE/
Journal: BULLETIN DE L INSTITUT PASTEUR, 1992, V90, N3 (JUL-SEP), P143-163
Language: FRENCH Document Type: REVIEW
Abstract: Poliomyelitis paralyses are caused by poliovirus(PV)-induced necrosis of motor neurons. It has been suggested that the virus is implicated in some degenerative diseases of the central nervous system such as the post-poliomyelitis syndromes. Three years ago, we showed that PV can persistently infect some human neuroblastoma cell lines. Mutated viruses with modified cell specificities were isolated several months after the inoculation of neuroblastoma cells. These mutants could persistently infect cells of neural as well as of non-neural origin. Such mutants could be of value for elucidating the interactions of PV with cells of the central nervous system. Persistently infected cells and the PV mutants selected in these cells constitute the first in vitro model for studying the possible implication of PV in some degenerative diseases of the central nervous system.

4/7/12 (Item 10 from file: 34)
DIALOG(R)File 34:SCISEARCH(R) CITED REF SCI
(c) 1999 INST FOR SCI INFO. All rts. reserv.

01795500 Genuine Article#: JC214 Number of References: 53
Title: A 45-YEAR-OLD MAN WITH CONFUSION, SEIZURES, AND FEW FOCAL FINDINGS - METASTATIC MALIGNANT-MELANOMA, ENCEPHALITIC FORM, IN LEPTOMENINGES AND

CEREBRAL-CORTEX
Author(s): GRUBER ML; DAVIS KR; SOBEL RA
Corporate Source: MASSACHUSETTS GEN HOSP,NEUROL/BOSTON//MA/02114; HARVARD UNIV,SCH MED/BOSTON//MA/02115
Journal: NEW ENGLAND JOURNAL OF MEDICINE, 1992, V327, N2 (JUL 9), P107-116
Language: ENGLISH Document Type: DISCUSSION

4/7/13 (Item 11 from file: 34)
DIALOG(R)File 34:SCISEARCH(R) CITED REF SCI

01637536 Genuine Article#: HN392 Number of References: 149
Title: **ADHESION MOLECULES** AND THE LIVER - FROM CELL BIOLOGY TO LIVER-DISEASE
Author(s): SCOAZEC JY; FELDMANN G
Corporate Source: UNIV PARIS 07,BIOL CELLULAIRE LAB,16 RUE HENRI HUCHARD/F-75877 PARIS 18//FRANCE/; UNIV PARIS 07,INSERM,U327/F-75877 PARIS 18//FRANCE/
Journal: GASTROENTEROLOGIE CLINIQUE ET BIOLOGIQUE, 1992, V16, N3 (MAR), P 264-277
Language: FRENCH Document Type: REVIEW

4/7/14 (Item 1 from file: 98)
DIALOG(R)File 98:General Sci Abs/Full-Text

04007241 H.W. WILSON RECORD NUMBER: BGSI99007241 (THIS IS THE FULLTEXT)
Quasispecies structure and persistence of RNA viruses.
Domingo, Esteban
Baranowski, Eric; Ruiz-Jarabo, Carmen M
Emerging Infectious Diseases (Emerging Infect Dis) v. 4 no4 (Oct./Dec. '98) p. 521-7
LANGUAGE: English
COUNTRY OF PUBLICATION: United States
WORD COUNT: 4724

ABSTRACT: Viral quasispecies are closely related (but nonidentical) mutant and recombinant viral genomes subjected to continuous genetic variation, competition, and selection. Quasispecies structure and dynamics of replicating RNA enable virus populations to persist in their hosts and cause disease. We review mechanisms of viral persistence in cells, organisms, and populations of organisms and suggest that the critical interplay between host and viral influences (including in some cases the quasispecies organization) is the main driving force for long-term survival of viruses in nature. Reprinted by permission of the publisher.

TEXT:

The emergence and reemergence of infectious diseases is influenced by the genetics of the infectious agents, the genetics of their hosts and potential new host species, and a considerable number of environmental factors (1-3). The current view proposes a strong stochastic (chance) component regarding the time, place, severity, and epidemiologic impact of infectious disease emergences (2,3). For RNA and possibly some DNA viruses, increasing evidence suggests that genetic variation (mutation, recombination, and genome segment reassortment in the case of multipartite genomes) affects adaptability to environmental changes (4-9). Since some types of adaptation involve changes in host cell specificity (5,6,10), genetic variation of viruses may be involved in the emergence of pathogenic viruses from apathogenic ancestors. Many studies over the last 2 decades have documented the unpredictability of genetic variation in viruses (2,5-7).

In this report, we consider viral persistence in connection with the population structure of RNA viruses, specifically, the extension (in space and time) of the pool of replicating genomes, which are a potential source

of variant viruses with altered biologic features. For example, hantaviruses are apathogenic and endogenous to several rodent species. In several geographic areas of the American continent, the unusually mild and wet (El Nino effect) spring seasons of 1992 and 1993 resulted in abundant food and coverage for deer mice, increased numbers of infected deer mice, and increased risk for human infections. These factors led to the newly recognized severe pulmonary syndrome of humans in 1993 (11). Like many pathogenic RNA viruses, hantavirus evolved in humans, and recent epidemiologic evidence suggests human-to-human transmission (12); whether human-to-human transmission is exceedingly rare or is an unusual property associated with Andes virus is not known. The number of carriers, their ability to transport virus (because of their mobility and absence of severe symptoms), and the viral load (number and concentration of infectious particles) in each carrier must be involved in viral emergences and reemergences (2-4,6,13).

POPULATION COMPLEXITY OF REPLICATING GENOMES: VIRAL QUASISPECIES

The viral load in an infected host is both static and dynamic. The static component can be divided into the total number of particles and the numbers and types of mutant viral genomes present in that total. Rather than being homogeneous, RNA virus populations consist of complex distributions of mutant (and sometimes also recombinant) genomes, in a type of population structure known as quasispecies (6,14-16). Assuming a random distribution of mutations among genomes, the number of variant genomes in a viral quasispecies increases dramatically with population size (15,17). For example, in a genome distribution with an average of five mutations per genome, the expected number of genomes with 20 mutations is 26 when the population size is 1X108 viral particles but reaches 2,600 when the population size is 2X1011 particles, as calculated from the Poisson distribution (17). Fitness variations of the individual mutants modify the actual number of genomes in each mutation class (6,14-17). In a horse infected with epizootic Venezuelan equine **encephalitis**, viral titers in blood reach a high of 108 infectious units (i.u.)/ml, or a total of approximately 3X1012 i.u. These high titers are probably needed for efficient transmission of the virus to insect vectors and for completion of the arbovirus life cycle (18). High titers are also reached in acute infections with HIV-1, hepatitis B virus (HBV, a hepadnavirus replicated by an error-prone polymerase through an RNA intermediate), hepatitis C virus (HCV), influenza virus, the animal foot-and-mouth disease virus (FMDV), and probably many others (7,8).

Increasing evidence indicates that quasispecies evolution may lead to the selection of virulent viruses and to the emergence of new viral pathogens (1-7,10,17,18). For example, a single site at the 5'-untranslated genomic region of coxsackievirus B3 was associated with its cardiovirulent phenotype. Swine vesicular disease, not reported before 1966, may represent a human coxsackie B5 variant adapted to swine. Specific mutations in the RNA of lymphocytic choriomeningitis virus can confer a viral tropism for neurons or for cells of the immune system. Evolution of measles virus can lead to hypermutated forms that have been associated with subacute sclerosing panencephalitis. Major human influenza pandemics have been associated with antigenic shift resulting from genome reassortment between a human influenza virus and an animal influenza virus. Some small DNA viruses possess considerable genetic heterogeneity within infected hosts. Canine parvovirus was probably derived from a feline parvovirus as a result of two amino acid replacements in the viral capsid (1-7,10,17,18).

The viral load during RNA virus replication also has a strong dynamic component. In persons infected with HIV-1, HBV, or HCV, an estimated 1010 to 1012 new virions are produced each day. For some microorganisms (not only viruses), in what has been termed short-sighted evolution of pathogenic microorganisms (19), virulence may be an inadvertent consequence of mutation and selection in the parasite population. Models of HIV-1 pathogenesis based on the continuous production of antigenic variants have been proposed (8,19,20). As the infection progresses the complexity of antigenically distinct mutants may overwhelm the immune system, leading to AIDS (20). Models of HIV-1 pathogenesis, based on the stimulation of

infected T-lymphocytes by secondary antigens (from opportunistic infections), have also been proposed; the progression of HIV infection to AIDS is still poorly understood. In HIV, and many other infections, the evolving viral quasispecies are exploring new mutant variants at astonishingly high rates. The balance between mutation rates and replication rounds is one of the reasons for the great adaptability of RNA viruses (6,7,14-17).

TYPES OF VIRAL PERSISTENCE

"Persistence," which refers to long-term survival of viruses in their hosts, has been described in at least three ways. 1) Long-term survival of virus within a viable cell population occurs when cell disease and destruction are limited and viral genomes replicate in balance with the multiplication of the host cells. 2) Survival of viruses in entire organisms can rarely be reduced to persistence in one cell type since organisms are built as sets of interconnected mosaics of cell types and cell protein effectors; persistence of viruses in organisms often means coping with multitudes of selective forces and defense reactions while allowing the host to survive. 3) A virus can be maintained in nature by the continuous infection of susceptible host organisms, with or without persistence in cells or organisms and with or without long-term stability of viruses as free particles. Genetic, ecologic, and environmental factors exert different influences on these types of persistence. The quasispecies structure of RNA viruses plays an obvious, positive role in some persistence mechanisms. In others the role is more subtle, marginal, or nonexistent. The observations summarized here suggest, however, that persistence is always the result of interactions between viral and host determinants.

PERSISTENCE OF VIRUSES IN CELLS

A variety of mechanisms enable viral genomes to replicate in balance with host cell multiplication. Most of the well-studied mechanisms of persistence of RNA viruses in primary cell cultures or established cell lines involve genetic variation of the virus, the cell, or both. One way to limit cell death is by generating and accumulating defective genomes. Defective genomes depend on a complementing, standard virus for replication; yet they may compete with that standard virus for cellular and viral gene products (which the virus needs to complete its life cycle and kill cells), thus increasing cell survival (21). A classic example is provided by defective interfering (DI) particles of vesicular stomatitis virus (VSV), and related viruses (22). During serial passage of VSV at high multiplicity of infection, DI particles accumulate in a cyclic pattern (23). Standard VSV and DI particles alternate in their dominance in a continuous process of mutant generation, competition, and selection. Excess virus leads to generation and accumulation of DI particles. With excess DI particles, mutant viruses able to escape interference rise to dominance (5). A feedback mechanism is established, which underlines the biologic relevance of the rapid evolutionary potential of RNA genomes (5).

Cell disease can also be limited by infecting cells with limited permissivity for the virus or by selecting noncytolytic variant viruses. In a number of cell-virus systems, cells and viruses coevolve, as documented for reovirus persisting in L cells (24) and for other RNA and DNA viruses (25-28). FMDV illustrates how the quasispecies structure initiates and maintains persistence (26,29). The presence in the FMDV quasispecies of variants with decreased ability to kill BHK-21 cells was not the mechanism (at least the prevailing mechanism) responsible for persistence. Rather, these experiments (29), which measured the proportion of cells that survived an initial cytolytic infection, indicated that a rapid variation of the cells initiated persistence. Indeed, the cells rapidly became more resistant to the infecting FMDV, and the virus became more virulent for the host BHK-21 cells (29). The quasispecies structure and consequent adaptability of RNA genomes do not justify any generalization on the participation of quasispecies, rather than the seemingly more static cellular DNA genomes, in initiation of viral persistence (29). However, the

rapid evolution of FMDV toward virulence was very likely facilitated by mutant generation and was essential to sustain persistence (26,29). When the carrier cultures were challenged with FMDVs of distinct degrees of virulence (a population replacement experiment), the endogenous persistent virus was replaced by the externally added virus only when the latter displayed a higher virulence for BHK-21 cells. Thus, virulence can be a positive trait in viral persistence (30), and virulent variants present in the FMDV quasispecies helped maintain persistence when the triggering cellular event had occurred (29,30).

PERSISTENCE OF VIRUSES IN ORGANISMS

Viral persistence in organisms requires a supply of susceptible cells replicating at the same pace as the virus and the ability to survive the host immune response. With RNA viruses, the continuous production of mutant viruses (inherent to the quasispecies dynamics 14,15) contributes to virus survival (2,5-7,15-17). Viruses often use alternative receptors and coreceptors, and one or a few amino acid substitutions at exposed surface sites may trigger a shift in receptor specificity (8,10,31). For HIV-1, amino acid substitutions at the surface glycoprotein may effect shifts in receptor use (10,31), and mutations at several genes may promote escape from antibodies or cytotoxic T lymphocytes (CTLs) (8,10); the generation of 109 to 1010 viral particles per day undoubtedly facilitates escape (8,20). Although evidence of positive (Darwinian) selection of escape mutants is firm, the quasispecies structure and dynamics predict genetic variation in the absence of immune selection (5,32). The two mechanisms are compatible.

Some viruses (HBV, HIV-1, FMDV, measles virus, herpesviruses) may persist after an acute infection, and the dose of infecting virus often determines either clearance or long-term persistence (8,33). Viruses transmitted vertically may induce immune tolerance and persist in adults (33). Viruses may also persist by being sequestered in some privileged sites of an organism, such as the central nervous system, partially hidden from immune attack (33). Ineffective antibody responses may be due to tolerance, immunosuppression (as a result of some infection, genetic disease, or immunosuppressive treatments), production of nonneutralizing antibodies, or cell-to-cell spread of virus not exposed to immune recognition (33). Viruses that infect lymphocytes or macrophages (HIV, cytomegalovirus, measles virus) may alter immune responses and thus facilitate their own persistence (8,33).

PERSISTENCE OF VIRUSES IN NATURE

All viruses have developed common functional and adaptive strategies; however, the strategies used by DNA and RNA viruses to evade host defenses have distinct features. RNA viruses often exploit mutation to achieve changes in host range and escape antibody and CTL responses (8,10,31,32). Because of their limited genetic complexity (which can be equated with the size of their genomes of 3 to 30 Kb), RNA viruses are generally tolerant to high levels of mutagenesis (6,14,16). In contrast, large DNA viruses (of the herpesvirus family, poxviruses, iridoviruses, adenoviruses) have complex genetic information; the need to maintain this information limits their tolerance to mutation. That simple genomes are generally more tolerant to mutagenesis than more complex ones can be argued on the basis of the higher mutation rates observed in simple replicons and the evolution of replication to include proofreading and postreplicative repair functions for the replication of DNA of cells and of at least some of the complex DNA viruses (5,6,14,16). Although antibody and CTL-escape mutants (as well as drug-resistant mutants) have also been described for DNA viruses, the latter have evolved alternative mechanisms to counteract host defenses (34,35). As examples, the adenovirus proteins E3/19K and E1a suppress surface molecules (MHC class I, class II, **adhesion molecules**) required for T-cell recognition. The Epstein-Barr virus BCRF1 protein is a host interleukin (IL)-10 homologue that activates the IL-10 receptor. Human cytomegalovirus encodes a protein structurally resembling the macrophage inflammatory protein 1a/RANTES receptor. Cytokines regulate immune and inflammatory responses and may trigger antiviral responses in organisms. It is not surprising that DNA viruses causing either persistent or acute

infections have evolved to encode homologues of the extracellular binding domains of cytokine receptors (34,35).

Phylogenetic analyses of herpesvirus genomes infecting a broad range of host animal species (the complete genomic nucleotide sequence of 18 herpesvirus genomes is known) suggest a possible cospeciation with their host organisms (36). The capture of cellular genes (and gene assemblies) by DNA viruses to counteract host defense responses agrees with the proposal of a modular origin of viruses (37,38) and has opened a new approach for analyzing new functions related to the immune response in differentiated organisms (35). The selective forces imposed by viral parasites may have contributed to a more rapid diversification of cellular proteins involved in host defense (34). In turn, coevolution may have relaxed the specificity of viral analogues of cellular effectors: the viral chemokines vMIP I and vMIP II of **herpes** simplex virus-8 bind to a broader range of cellular chemokine receptors (although with lower affinity) than their cellular homologues (39). Genes that have strong sequence identity with cellular counterparts are also encoded by RNA viruses (e.g., sarcoma and leukemia viruses) (34) that tend to exchange genetic material with their hosts. However, evasion strategies based on gene capture and protein mimicry are dominant in DNA viruses, and strategies based on mutant production are widespread among RNA viruses (6-8,16,17,34,35).

PERSISTENCE OF VIRUSES AT THE POPULATION LEVEL

To be maintained in nature and avoid extinction, viruses must have susceptible hosts as well as adaptability to a range of biologic environments (6). Even persistence in an individual host would not help long-term persistence of a viral pathogen in nature, without a number of additional influences (13,19,40), such as the possibility of transmission within the same host species (sexual, perenteral, or respiratory routes) or to a different host species (13,40). Human rhinoviruses do not persist in their hosts and succeed (supported by the high frequency of common colds) in continuous reinfections through aerosols transmission (or other contacts). In the other extreme of life cycle complexity, arboviruses sequentially infect a number of disparate hosts. As an example, insects can transmit Venezuelan equine **encephalitis** virus between horses and other mammalian species and can also infect humans, the dead-end point of a complex infectious cycle (18). Evidence indicates that a few point mutations in the viral genome may be sufficient to upset the balance of viral loads in enzootic cycles, render the virus epizootic, and cause severe outbreaks (18). In La Crosse virus, an important cause of pediatric **encephalitis**, the virus persists in cells of the midgut epithelium of Aedes triseriatus. The virus is transovarially transmitted and survives transeasonally in the diapausing mosquito embryo. In quiescent ovaries there is reduced viral replication with limitations in the host-derived 5'-mRNA sequences that prime viral transcription (41). Long-term survival at the population level is associated with persistence and limitation of virulence in the vector mosquito. The complex arboviral life cycle appears to require the fine tuning of a number of factors: the amount of virus in viremia and the duration of viremia, which are likely to contribute to the efficient uptake of virus by the vectors (18), and replication and stability of the virus in the vectors to ensure infection of the mammalian host (18). Perturbations in these, and probably other factors, could lead to viral extinction. What prevents viral extinction? Again, all evidence points to genetic factors of the virus and the hosts together with environmental and ecologic influences (1,3,5-7,17,18). Virus variants unable to fulfill the required processes with the correct timing may be generated, but they would be selected against. We can study only successful examples. Virus variants that do not complete a complex life cycle are yet another example of negative selection (elimination of suboptimal viruses). Negative selection is one of the forces preserving virus variants that are fit in relation to the interactions with their hosts (6,7,14-17,32), a force we believe is responsible for maintaining (at least to some extent) the identity of RNA viruses as disease-causing agents.

The stability of virus particles may also play a relevant role in

successful transmission, as documented in aerosol transmission, airborne spread, or mechanical transport of viruses by insects (42). An example is provided by FMDV. In spite of its lability at mildly acidic pH and at moderate temperatures, FMDV is resistant to desiccation and can be transported on dust particles over long distances. Most spectacular is the case of the highly complex and host-specific baculoviruses. They form rod-shaped virions occluded in large capsules made of a viral-coded matrix protein termed polyhedrin. Capsules are uptaken by the insects (of the orders Lepidoptera and Hymenoptera) and are dissolved by midgut epithelial cells. Thus, capsule formation is responsible for the spread of the virus in the insect population. Again, a great diversity of mechanisms (as varied as those seen at the level of individual organisms or of the cells) operate to ensure viral persistence at the population level.

BASIC ISSUES

The mutant distributions that compose viral quasispecies are the raw material on which selective forces and random sampling events act in the molecular evolution of RNA viruses (5-7,14-18,32,38). In addition to constituting a basic adaptive strategy, the quasispecies genetic organization has a number of biologic implications (5-9,16,32,43), some of which have a direct bearing on viral persistence. It has been wrongly argued that if quasispecies distributions were involved in virus persistence, all RNA viruses would establish persistent infections but that on the contrary, only a minority do. We hope to have shown that persistent infections are unavoidably, necessarily, and evidently the result of an interplay between viruses and their hosts (44). Thus, a quasispecies structure does not imply necessarily that the virus will produce a persistent infection. A potent CTL response may clear a virus infection provided that the viral load has a size amenable to clearing, and this may occur whether the virus is a complex quasispecies or not. In contrast, a similar CTL response confronting a high viral load may frequently fail to clear the infection; in this failure, the presence (in a dynamic quasispecies) of CTL-escape mutants (and many other types of mutants with biologically deviant properties) may be crucial for virus survival, including the establishment of persistence or chronicity. Also, increasing evidence suggests that viruses thought not to persist, such as poliovirus, may actually do so; late postpoliomyelitis syndromes may be one consequence (33, 42). Even with the available analytical technology, total clearing of an infecting virus from an organism cannot be guaranteed.

The issue is clear: either we design new antiviral strategies that take into consideration the quasispecies structure of RNA viruses (6,9,43), or viral diseases (classical, new, or reemergent) will remain difficult to control.

Added material

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4/7/15 (Item 1 from file: 266)
DIALOG(R)File 266:FEDRIP

00313915
IDENTIFYING NO.: 2R01EY05945-13 AGENCY CODE: CRISP
CYTOTOXIC LYMPHOCYTES IN HSV1 CORNEAL LESIONS
PRINCIPAL INVESTIGATOR: HENDRICKS, ROBERT L

ADDRESS: UNIVERSITY OF PITTSBURGH 203 LOTHROP STREET PITTSBURGH, PA 15213
PERFORMING ORG.: UNIVERSITY OF PITTSBURGH AT PITTSBURGH, PITTSBURGH, PENNSYLVANIA
SPONSORING ORG.: NATIONAL EYE INSTITUTE
FY : 1999 TYPE OF AWARD: Competing Continuation (Type 2)
SUMMARY: **Herpes** simplex virus (HSV) is a common pathogen in humans. Corneal inflammation and scarring is a potentially blinding complication of HSV-1 ocular infections in patients who appear to be immunologically normal. When a patient becomes immunologically compromised, an HSV-1 infection that is normally localized can disseminate to a variety of organs including the brain, where it can cause a lethal **encephalitis**. Due to the ability of the virus to be transmitted across tight cellular junctions with minimal exposure to the extracellular space, antibodies tend to be ineffective at halting the spread of the virus. Cytotologic T lymphocytes (CTL) are capable of recognizing processed vital proteins early in the infectious process prior to production of new virus particles. For this reason, cytotoxic function is considered to be an important component of the host defense against HSV-1 infections. However, surprisingly little is known about the mechanisms that control CTL function within the microenvironment of the infected tissue. Recent evidence suggests that individual CTL clones may vary in their requirements for accessory molecule expression on target cells. Moreover, the array of accessory molecules that is expressed may vary on target cells derived from different tissues. The regulation of CTL activity in HSV-1 infected tissue is further complicated by the fact that the virus itself may inhibit presentation of its own antigens to T cells by blocking the transmission of MHC class 1 molecules to the cell surface.

For these reasons, we believe that the potential for CTL protection can only be evaluated when their activity is measured under conditions that mimic the microenvironment of the infected tissue of interest. The proposed studies will investigate the interaction and cross-regulation among CTL, tissue cells, and HSV-1 in the mieroenvironment of infected eyelids and corneas. We will employ three approaches to define these interactions: (1) define phenotypic changes that occur in the CTL precursors as they differentiate into active cytotoxic cells, and where in their progress from lymph nodes to the infected tissue differentiation occurs; (2) evaluate the ability of cells derived from cornea and eyelid tissues to serve as targets for CTL, the accessory molecules that contribute to the interaction, and how the interaction is regulated by HSV-1 infection and cytokines that are present in the infected tissues; (3) determine if cells from infected tissue can influence the process of CTL differentiation. To our knowledge these studies represent the first attempt to characterize HSV-specific CTL function in a system that recognizes the regulatory influences that may be uniquely expressed in a specific HSV-1-infected tissue. We believe that these investigations are justified by the enormous potential of CTL for controlling the dissemination of the virus with minimal immunopathology in these sensitive tissues.

2/7/1 (Item 1 from file: 73)
DIALOG(R)File 73:EMBASE

07278044 EMBASE No: 1998180978
Evidence for deficiencies in intracerebral cytokine production, adhesion molecule induction, and T cell recruitment in **herpes** simplex virus type-2 infected mice
Lewandowski G.; Hobbs M.V.
G. Lewandowski, Virion Systems, Inc., 9610 Medical Center Drive, Rockville, MD 20850 United States
Journal of Neuroimmunology (J. NEUROIMMUNOL.) (Netherlands) 1998, 81/1-2 (58-65)
CODEN: JNRID ISSN: 0165-5728
PUBLISHER ITEM IDENTIFIER: S0165572897001598
DOCUMENT TYPE: Journal; Article
LANGUAGE: ENGLISH SUMMARY LANGUAGE: ENGLISH
NUMBER OF REFERENCES: 34

We examined the intracerebral T cell response in mice infected with neurovirulent HSV-2 strains and an avirulent HSV-1. In HSV-2-infected brains, (i) IL-beta, TNF-alpha and IFN-gamma, mRNA expression was low, (ii) ICAM-1 and **VCAM**- 1 were not induced, (iii) few CD4sup + or CD8sup + cells were detected. By contrast, in HSV-1-infected brains, (i) cytokine mRNA expression was high, (ii) adhesion molecules were strongly expressed, (iii) many T cells were detected. We suggest that deficient T cell extravasation into HSV-2-infected brain regions is caused by negligible ICAM-1 and **VCAM**-1 expression, which is due to low expression of critical cytokines.

2/7/1 (Item 1 from file: 73)
DIALOG(R)File 73:EMBASE

07278044 EMBASE No: 1998180978

Evidence for deficiencies in intracerebral cytokine production, adhesion molecule induction, and T cell recruitment in **herpes** simplex virus type-2 infected mice

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Journal of Neuroimmunology (J. NEUROIMMUNOL.) (Netherlands) 1998, 81/1-2 (58-65)
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s (herpes) and (encephalitis) and (adhesion(w)molecule?)

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          115721  HERPES
           48261  ENCEPHALITIS
          255260  ADHESION
          627877  MOLECULE?
           71181  ADHESION(W)MOLECULE?
      S3      10  (HERPES) AND (ENCEPHALITIS) AND (ADHESION(W)MOLECULE?)
? rd s3

...completed examining records
      S4       5  RD S3 (unique items)
? t s4/7/all
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4/7/1 (Item 1 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

09684805 BIOSIS NO.: 199598139723
Adhesion molecule expression and lymphocyte adhesion to cerebral endothelium: Effects of measles virus and **herpes** simplex 1 virus.
AUTHOR: Brankin B(a); Hart M N; Cosby S L; Fabry Z; Allen I V
AUTHOR ADDRESS: (a)Div. Neuropathol., Queen's Univ. Belfast, Inst. Clinical Sci., Grosvenor Road, Belfast BT12 6BL**UK
JOURNAL: Journal of Neuroimmunology 56 (1):p1-8 1995
ISSN: 0165-5728
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: Expression of endothelial cell (EC) **adhesion molecules** is increased in inflammatory neurological disorders and this may regulate lymphocyte homing to the central nervous system (CNS). Viral **encephalitis** is characterized by lymphocytic infiltration of the CNS and one mechanism of this response may be EC **adhesion molecule** induction with consequent inflammatory cell/EC binding. This report characterizes the effects of **herpes** simplex 1 (HSV1) or measles virus (MV) infection of BALB/c brain microvascular EC in vitro on adhesion of naive syngenic splenocytes and levels of ICAM-1. Adhesion was enhanced by 42% for MV-infected cells and by 73% for HSV-1-infected EC. At the multiplicities of infection employed, levels of ICAM-1 were upregulated on HSV-1-infected EC, but not on MV-infected EC. It is concluded that ICAM-1/ligand interactions do not play a role in mediation of MV enhancement of adherence, but represent one mechanism responsible for increased lymphocyte adherence to HSV-1-infected cerebral EC.

4/7/2 (Item 2 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

06455812 BIOSIS NO.: 000037027823
INTERCELLULAR **ADHESION MOLECULE**-1 ICAM-1 IN CENTRAL NERVOUS SYSTEM CNS IMMUNOPATHOLOGY
AUTHOR: SOBEL R A; MITCHELL M; ROTHLEIN R
AUTHOR ADDRESS: MASS. GEN. HOSP., HARV. MED. SCH., BOSTON, MASS. 02114.
JOURNAL: 73RD ANNUAL MEETING OF THE FEDERATION OF AMERICAN SOCIETIES FOR EXPERIMENTAL BIOLOGY, NEW ORLEANS, LOUISIANA, USA, MARCH 19-23, 1989. FASEB

(FED AM SOC EXP BIOL) J 3 (4). 1989. A1320.
CODEN: FAJOE
DOCUMENT TYPE: Meeting
RECORD TYPE: Citation
LANGUAGE: ENGLISH

4/7/3 (Item 1 from file: 73)
DIALOG(R)File 73:EMBASE

07278044 EMBASE No: 1998180978
Evidence for deficiencies in intracerebral cytokine production, **adhesion molecule** induction, and T cell recruitment in **herpes** simplex virus type-2 infected mice
Lewandowski G.; Hobbs M.V.
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Journal of Neuroimmunology (J. NEUROIMMUNOL.) (Netherlands) 1998, 81/1-2 (58-65)
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DOCUMENT TYPE: Journal; Article
LANGUAGE: ENGLISH SUMMARY LANGUAGE: ENGLISH
NUMBER OF REFERENCES: 34

We examined the intracerebral T cell response in mice infected with neurovirulent HSV-2 strains and an avirulent HSV-1. In HSV-2-infected brains, (i) IL-beta, TNF-alpha and IFN-gamma, mRNA expression was low, (ii) ICAM-1 and VCAM- 1 were not induced, (iii) few CD4sup + or CD8sup + cells were detected. By contrast, in HSV-1-infected brains, (i) cytokine mRNA expression was high, (ii) **adhesion molecules** were strongly expressed, (iii) many T cells were detected. We suggest that deficient T cell extravasation into HSV-2-infected brain regions is caused by negligible ICAM-1 and VCAM-1 expression, which is due to low expression of critical cytokines.

4/7/4 (Item 2 from file: 73)
DIALOG(R)File 73:EMBASE

06013607 EMBASE No: 1995042411
Involvement of LFA-1 and ICAM-1 in the herpetic disease resulting from HSV-1 corneal infection
Dennis R.F.; Siemasko K.F.; Tang Q.; Hendricks R.L.; Finnegan A.
Department of Ophthalmology, Rush-Presbyterian-St Luke's Med Ctr, 1753 West Congress Parkway,Chicago, IL 60612 United States
Current Eye Research (CURR. EYE RES.) (United Kingdom) 1995, 14/1 (55-62)
CODEN: CEYRD ISSN: 0271-3683
DOCUMENT TYPE: Journal; Article
LANGUAGE: ENGLISH SUMMARY LANGUAGE: ENGLISH

Herpes simplex virus type 1 (HSV-1) corneal infection in immunologically normal mice results in a transient epithelial lesion followed in about 2 weeks by a potentially blinding inflammatory response in the corneal stroma, and a mild blepharitis. Similarly infected T cell-deficient mice do not develop corneal stromal inflammation, but exhibit severe periocular skin disease and succumb to viral **encephalitis**. The role of certain **adhesion molecules** in both T cell activation, and in the extravasation of inflammatory cells from the blood into inflammatory sites is now being established. These studies investigated the involvement of the adhesion pair LFA-1/ICAM-1 in the disease that results from HSV-1 corneal infection in mice. Treatment of mice with mAb to LFA-1 beginning 1 day before HSV-1 corneal infection

resulted in a delay in the onset of stromal inflammation, but ultimately stromal inflammation developed to a normal extent. This treatment also caused a significant exacerbation of periocular skin disease, but did not render mice susceptible to **encephalitis**. Treatment with mAb to ICAM-1 beginning 1 day before HSV-1 corneal infection caused an acceleration of both stromal inflammation and periocular skin disease, and rendered mice uniformly susceptible to lethal **encephalitis**. Treatment with either mAb beginning 6 days after HSV-1 corneal infection did not significantly affect the clinical course of herpetic disease. Our findings suggest that LFA-1 may play a role in the early phase of corneal stromal inflammation following HSV-1 corneal infection. Both LFA-1 and ICAM-1 appear to be important for protection of the skin from HSV-1 infection. ICAM-1 but not LFA-1 is necessary for protection from **encephalitis** following corneal infection.

4/7/5 (Item 1 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

09620479 98382030
Telencephalin as an indicator for temporal-lobe dysfunction [letter]
Rieckmann P; Turner T; Kligannon P; Steinhoff BJ
Lancet (ENGLAND) Aug 1 1998, 352 (9125) p370-1, ISSN 0140-6736
Journal Code: L0S
Languages: ENGLISH
Document type: LETTER

00017443

The FDA's New Procedures for the Use of Investigational Drugs in Treatment (SPECIAL COMMUNICATIONS)

YOUNG, FRANK E.; NORRIS, JOHN A.; LEVITT, JOSEPH A.; NIGHTINGALE, STUART L.

JAMA, The Journal of the American Medical Association

10/3/3 (Item 3 from file: 442)
DIALOG(R)File 442:AMA Journals

00097485

Herpesviruses in **Multiple Sclerosis** (ARTICLE)

Archives of Neurology
Feb, **1996**; Editorial: tzn123

10/3/4 (Item 4 from file: 442)
DIALOG(R)File 442:AMA Journals

00097474

Herpes Simplex Virus in Postmortem **Multiple Sclerosis** Brain Tissue (ARTICLE)

SANDERS, VIRGINIA J.; WADDELL, AIMEE E.; FELISAN, STEPHEN L.; LI, XIMING; CONRAD, ANDREW J.; TOURTELLOTTE, WALLACE W.
Archives of Neurology
Feb, **1996**; Original Contribution: tzn125
LINE COUNT: 00518